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Archives of Internal Medicine

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OBSERVATIONS ON THE OCCURRENCE OF INVERTED AND DIPHASIC P-WAVES IN LEAD III OF THE HUMAN ELECTROCARDIOGRAM *

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Apart from the inversion of the P-wave met with in Lead III in the human electrocardiogram in the presence of an ectopic, heterogenetic rhythm,[1] associated with a definite change in the location of the pacemaker, and as a result of disturbances in the respiratory rhythm, such negativity of the atrial deflection is but occasionally seen, though it has seemed to us that the frequency of its incidence in this derivation in pathologic hearts is greater than one is led to expect from a review of the literature.

That Lead III shows the greatest susceptibility to these changes of form and direction is a fact of common observation, and the frequent inversion of the T-wave seen in this lead in otherwise normal galvanometric curves is additional evidence of the variation in electrical negativity met with in clinical observations.

It has been shown by Einthoven, Fahr and de Waart[2] that the P-deflection in the third lead of the electrocardiogram may be conspicuously modified by the phases of respiration, being lower at the end of inspiration and beginning expiration, coinciding in this respect with the longer pauses of the cardiac cycle. They state that following a long pause in this lead (L_3) "P may appear of lower voltage (klein), at times diphasic, and again wholly negative, while following the short pauses, that is with greater cardiac frequency and diminished vagus tone, P again assumes its normal form and size." They further caution against the difficulties encountered in attributing these changes purely to the influence of respiration, because of the effect of the change in the position of the heart that comes into play. Assuming

* Submitted for publication Aug. 13, 1918.

* From the Medical Clinic of the Cleveland City Hospital and the Western Reserve University.

1. Lewis, T.: Quart. J. Med., **6**:221, 1913; Idem., Heart, **2**:23, 1910.

2. Einthoven, W., Fahr, G., and de Waart, A.: Pfluger's Arch. f. d. ges. Physiol., **150**:175, 1913.

as an added factor in the explanation of this change in the P-wave "that a slight rotation of the heart about the sagittal axis of the body, as is possible with a deep inspiration, is sufficient to modify conspicuously the form and height of the various complexes."

As bearing on the negativity of P in Lead III, the suggestions of Hering[3] in reference to the curves seen in *situs transversus* are of interest, only in so far, however, as they may apply to the inversion of P in this lead (L_3). This observer advances the theory that the invert P in true congenital dextrocardia may be due to the fact that the excitation wave in the transposed heart arises from a focus lying nearer that lead from which under normal conditions it is furthest away. Thus explaining the reversal of negativity on the purely physical basis of the relationship of the heart to the sagittal axis in a given lead. It should be recalled that in *situs transversus* this inversion of negativity affects Lead I alone. In this connection the interesting papers by Samojlhof[4] may be referred to.

In their experimental work on the dog's heart, Lewis, Meakins and White[5] have demonstrated a migration of the pacemaker within the S-A node following vagal stimulation, associated with a shortening of the conduction time between the leads employed and characterized by negative galvanometric curves. Further observations on alterations in the P-deflections following experimental vagus stimulation have been described by Einthoven[6] and by Meek and Eyster,[7] who have also studied the effect of such stimulation on the location of the pacemaker.

In reporting three cases characterized by an inversion of the P-wave associated with respiration, Wilson[8] has ascribed the negativity of P as due to a change in the location of the pacemaker, and has divided these changes into three classes: migration within the sinus node, or its immediate neighborhood, migration from the S-A node to the A-V node, and, third, escape of the idioventricular rhythm.

In alluding to similar inverted P-waves seen in Lead III, Wilson and Robinson[9] advance the view that this inversion is analagous to the changes that may occur in the experimental animal under vagal stimulation.

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3. Hering, H. E.: Prag. med. Wchnschr., **10**:133, 1911; cited by Kahn (Footnote 14).
4. Samojlhof, A.: Pfluger's Arch. f. d. ges. Physiol., **153**:196, 1913; Idem., Zentralbl. f. Herz u. Gefasskrankh., **6**:201, 1914.
5. Lewis, T., Meakins, J., and White, P. D.: Phil. Tr. Roy. Soc. London, 1914, Series B., pp. 205, 375.
6. Einthoven, W.: Arch. f. d. ges. Physiol., **122**:517, 1908.
7. Meek, W. J., and Eyster, J. A. E.: Heart, **5**:227, 1914.
8. Wilson, F. N.: Archives Int. Med., **16**:989, 1915.
9. Wilson, F. N., and Robinson, G. C.: Archives Int. Med., **21**:166, 1918.
10. Goddard, C. H.: Archives Int. Med., **16**:631, 1915.

In a paper on the changes in the P-wave in the human electrocardiogram, Goddard[10] has noted the greater frequency of these seen in Lead III, P_1 being inverted in but four, P_2 in but seven and P_3 in seventy-five of the total of his series of 700 cases. Whether or not the inversion of P in Leads I, II and III was associated with any change in conduction time is not stated, and as there is no statement as to the effect of atropin or digitalis on these inverted P-waves, it is difficult to classify them.

Following right vagal stimulation, conspicuous alteration in the form of the P-wave seen in Lead II has been noted by Ritchie.[11]

In his fundamental paper on the effect of digitalis on the human electrocardiogram Cohn[12] has shown that the inversion of T seen under the effect of digitalis may be influenced by atropin; that when, after a course of digitalis, the T-wave fails to show the usual reversal, this may be masked by the inhibitory effect of the vagi, and then after atropin T becomes more negative or inverted. The altered T-wave which atropin fails to affect he attributes to the action of the digitalis on the cardiac muscle. Cohn does not describe any change in the P-wave in Lead III, following digitalis, such as we have observed.

DETAILED REPORT OF ELECTROCARDIOGRAMS

In abstracting the case reports of the individuals on whom this study is based we have omitted as irrelevant all details as to the history and clinical course, giving only the clinical diagnosis, together with such notes as are essential in the interpretation of the figures.

CASE 1.—J. G., aged 72. Clinical diagnosis: complete atrioventricular dissociation with Stokes-Adams syndrome, known to be of two years' duration. The patient was admitted to the hospital again in November, 1917.

Electrocardiograms: Records taken in May, 1916, showed no abnormalities in the P-wave. In the records taken the day after admission, Nov. 5, 1917, all P-waves are upright[13] in the three leads.

After taking 4 c.c. of tincture of digitalis daily for ten weeks with absolutely no symptoms of disturbance, P_3 is diphasic or inverted, but becomes upright immediately after the administration of 2 mg. of atropin (Fig. 1, A, and B).

Records taken two months after digitalis had been discontinued show P_3 regularly upright.

Summary: Inverted and diphasic P_3 following the administration of digitalis, rendered upright by atropin.

CASE 2.—W. S., aged 62, No. 279. Clinical diagnosis: chronic myocarditis with intraventricular block.

Electrocardiograms: In the records taken before the administration of digitalis the P-wave was upright in all three leads. Records taken after 77.5 c.c. of tincture of digitalis had been given showed an inverted or a

11. Ritchie, W. T.: Quart. J. Med., **6**:47, 1912.

12. Cohn,, A. E.: J. Exper. Med., **21**:593, 1915.

13. We use the words "upright" and "inverted" as synonymous with positive and negative, a positive wave representing primary base negativity, and a negative wave primary apex negativity.

diphasic P_3. But in the records taken the next day, twenty-four hours later, after 87.5 c.c. of digitalis, P_3 was regularly upright. Atropin was not given at the time of the inversion (Fig. 2, A and B).

Summary: Transient inverted and diphasic P_3 occurring during the administration of digitalis. P-R interval 0.16 sec. with both upright and inverted P_3.

Case 3.—J. K., aged 59, No. 345. Clinical diagnosis: chronic myocarditis, probably luetic in origin.

Electrocardiograms: Normal mechanism; left ventricular preponderance; S_3 notched. T_1 small and upright; T_2 and T_3 inverted. P_3 inverted or diphasic. P-R interval in Leads I and II, 0.16 sec. P-R interval in Lead III, with invert P, 0.12 sec.

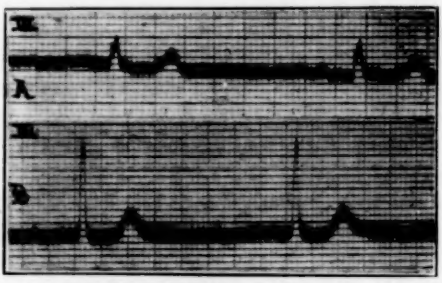

Fig. 1.—Case 1. Lead III. Complete a-v dissociation. A, P_3 inverted following digitalis. B, after atropin P_3 upright. In this as in all the figures, one division of ordinates equals 0.04 sec.

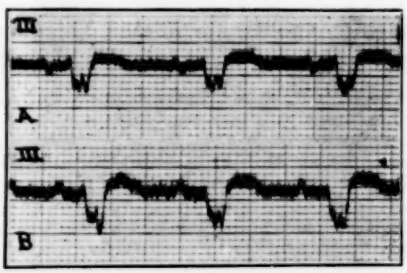

Fig. 2.—Case 2. Lead III. A, after 77.5 c.c. of digitalis P_3 inverted or diphasic. P-R interval 0.16 sec. with both upright and inverted P_3. B, twenty-four hours later, after 87.5 c.c. of digitalis P_3 upright.

P_3 was probably rendered upright by 2 mg. of atropin, though the curves are ragged (Fig. 3, A and B).

After 14 c.c. of tincture of digitalis, P_3 was definitely upright and remained so during the administration of digitalis (Fig. 3, C).

Record taken at the time of discharge, eight days after the last digitalis had been given, showed a variable P_3, upright, diphasic or inverted (Fig. 3, D).

Summary: Inverted or diphasic P_3, rendered upright by atropin, becoming inverted again after recovery from the atropin, then rendered upright by the administration of digitalis and remaining upright throughout its administration, becoming again variable eight days after the last digitalis had been given, when it appears upright, diphasic or inverted.

CASE 4.—M. J., aged 55, No. 364. Clinical diagnosis: chronic myocarditis, cardiac hypertrophy, arteriosclerosis.

Electrocardiograms: Normal mechanism; left ventricular preponderance. T_1 and T_2 inverted. T_3 upright. P_3 diphasic or inverted. P-R interval 0.25 sec. in all three leads.

P_3 is not altered by digitalis or by atropin (Fig. 4).

Summary: Permanent inverted or diphasic P_3 not induced by or affected by digitalis and not affected by atropin.

CASE 5.—W. T., aged 44, No. 342. Clinical diagnosis: chronic mitral endocarditis with myocardial failure. Died. No necropsy permitted.

Electrocardiograms: Normal mechanism. Occasional premature contractions, ventricular in origin. Left ventricular preponderance. P-waves upright in all three leads. P-R interval 0.22 sec. (Fig. 5, A).

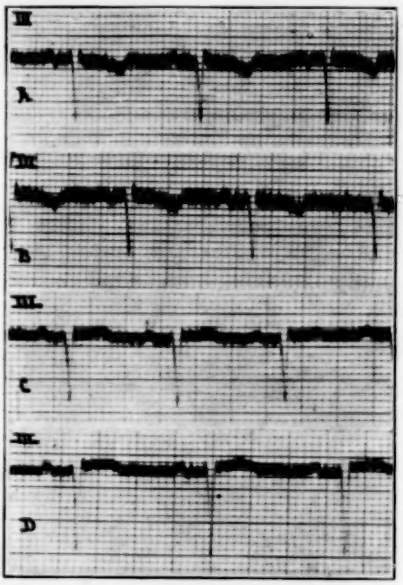

Fig. 3.—Case 3. Lead III. A, before digitalis, P_3 inverted and diphasic. P-R interval 0.12 sec. B, after atropin, P_3 probably upright, curves ragged. C, after 14 c.c. of digitalis, P_3 upright. D, eight days after last digitalis, P_3 variable, upright, inverted and diphasic.

After 18 c.c. of tincture of digitalis, P_3 was definitely inverted. The P-R interval measures 0.17 sec. (Fig. 5, B).

Fifteen minutes after 2 mg. of atropin P_3 became upright and remained so. P-R interval 0.18 sec. (Fig. 5, C).

Summary: A case in which the P-wave in Lead III was definitely inverted by digitalis, associated with a shortening of the conduction time, and this inversion was overcome by atropin.

CASE 6.—J. B., aged 46, No. 355. Clinical diagnosis: chronic myocarditis with transient right bundle-branch lesion.

Electrocardiograms: Typical right-bundle branch lesion curves on admission with inverted P_3. The P-R interval measures 0.12 sec. in all three leads (Fig. 6, A).

After 2 mg. of atropin the inverted P_3 became upright. P-R interval 0.12 sec. (Fig. 6, B).

Twenty-four hours later, after 10 c.c. of tincture of digitalis had been given the duration of the QRS complex had shortened and the notching of the initial ventricular deflections had disappeared. P_3, however, remains still inverted (Fig. 6, C).

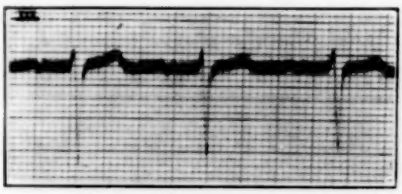

Fig. 4.—Case 4. Lead III. P-R interval 0.25 sec. in all three leads. P_3 permanently inverted or diphasic.

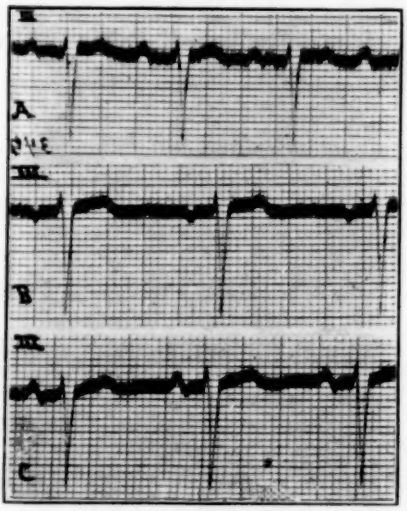

Fig. 5.—Case 5. Lead III. Before digitalis P-R interval 0.22 sec. A, P_3 upright. B, after 18 c.c. of digitalis P_3 inverted. P-R interval 0.17 sec. C, after atropin P_3 upright.

Twenty-four hours later, after 20 c.c. of digitalis had been given, P_3 was upright and still remained so seven days after the digitalis had been discontinued (Fig. 6, D).

Summary: A case of temporary defect in conductivity of the right bundle branch, showing a variability in P_3, apparently due to vagus influence. Following the general change in the electrical complex P_3 gradually became upright and remained so, this reversion apparently being due to digitalis.

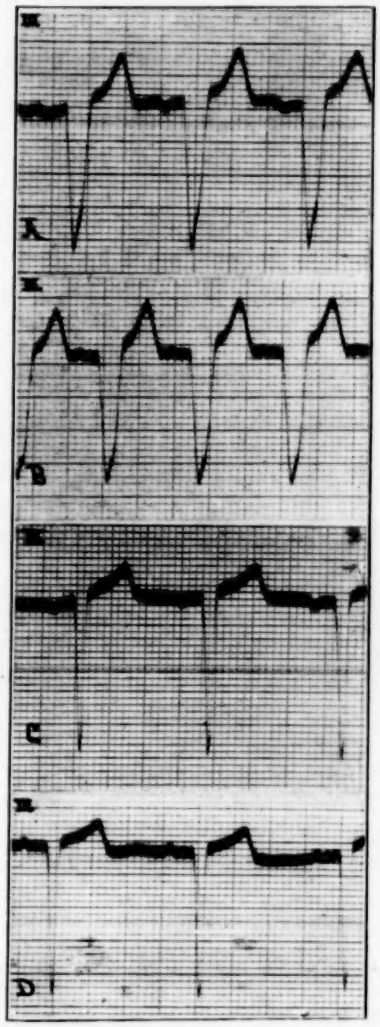

Fig. 6.—Case 6. Lead III. Transient right branch bundle lesion. A, before digitalis, P_3 inverted. P-R interval 0.14 sec. QRS complex measures 0.14 sec. B, after atropin, P_3 upright. P-R interval 0.10 sec. C, twenty-four hours later, after 10 c.c. of digitalis P_3 still inverted. QRS complex measures 0.08 sec. D, twenty-four hours later, after 20 c.c. of digitalis P_3 upright.

CASE 7.—O. B., aged 45, No. 351. Clinical diagnosis: cardiorenal disease with myocardial failure; tabes dorsalis.

Electrocardiograms: Very low voltage; notched R and S, conspicuous in Lead II. All T- and P-waves upright. P-R interval measures 0.14 sec. in all three leads (Fig. 7, A).

After 96 c.c. of tincture of digitalis had been given, with absolutely no symptoms referable to the drug, there was a complete A-V dissociation with an irregular inversion of P_3 (Fig. 7, B).

Thirty minutes after 2 mg. of atropin the mechanism was normal with a diphasic P_3. The P-R interval averaged 0.17 in Leads II and III. Twelve hours later P_3 was definitely upright (Fig. 7, C).

Summary: The production of a complete dissociation by digitalis with an inversion of P_3. Restoration of the normal mechanism and reversion of P_3 promptly induced by atropin.

CASE 8.—T. L., aged 16, No. 266. Clinical diagnosis: chronic mitral endocarditis, chronic pericarditis, rheumatic in origin.

Electrocardiograms: Normal mechanism. Occasional premature atrial systoles associated with an inverted P in all three leads. P_3, however, is con-

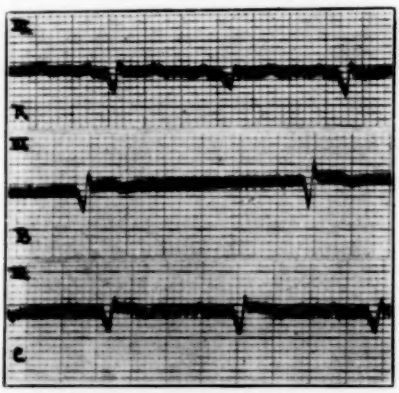

Fig. 7.—Case 7. Lead III. B, after 96 c.c. of digitalis, complete a-v dissociation with irregular inversion of P_3. C, after atropin, normal mechanism with diphasic P_3.

stantly inverted, remaining so in the absence of, as well as in the presence of, the extrasystoles. The P-R interval in Leads I and II during the normal mechanism measures 0.14 sec. With the occurrence of the extrasystole it is shortened, measuring 0.12 sec. In Lead III the P-R interval measures constantly 0.12 sec., being the same in the presence of the extrasystole and during the normal mechanism. In Fig. 8, A and B, we give both Lead II and III to show this dissimilarity (Fig. 8, A and B).

The administration of 12 c.c. of tincture of digitalis produced marked physiologic effect, with a coupled rhythm, but had no effect on the inverted P_3. The administration of 2 mg. of atropin had no effect on the inverted P_3. Vagus pressure was also without effect.

Records taken twenty days after the discontinuance of the digitalis showed P_3 inverted as before (Fig. 8, C).

Summary: This patient was under observation for over a year, having been admitted to the hospital, in all, four times in the previous fourteen months. On all previous admissions P_3 was always inverted. This case illustrates the

presence of a persistent inverted P_3 occurring in a pathologic myocardium, not related to digitalis action and also unaffected by atropin or by vagus pressure. In records taken two months later the extrasystoles were absent. P_3 was still inverted.

Case 9.—A. K., aged 25, No. 330. Clinical diagnosis: chronic endocarditis of the mitral valve and extreme decompensation; mitral stenosis.

Electrocardiograms: Normal mechanism. Right ventricular preponderance. P-waves upright in all three leads; broad and bifurcated in Leads I and II, typical of the form seen in mitral stenosis.

After the administration of 85 c.c. of tincture of digitalis, T_1 remained upright, T_2 and T_3 were inverted. The P-R interval measured 0.22 sec. (Fig. 9, A).

Seven days after the foregoing record was taken and ten days after the digitalis had been discontinued the broad and notched P-waves in Leads I

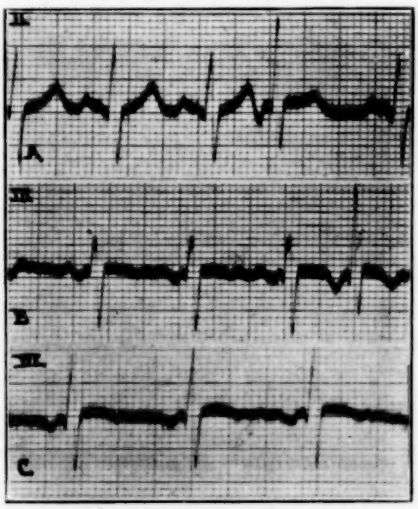

Fig. 8.—Case 8. Leads II and III. P-R interval 0.12 sec in all three leads. P_3 permanently inverted. A, to show extrasystole in Leads II and III. C, twenty days after last digitalis.

and II had disappeared and P_3 was definitely inverted. The P-R interval in Leads I and II measured 0.17 sec. In Lead III with the invert P, 0.11 sec. (Fig. 9, B).

Summary: A case showing a variation in the P-waves, with inversion of P_3 ten days after the discontinuance of digitalis. The relation of the invert P_3 to digitalis or to vagus effect is not definitely known, but on admission six weeks later P_3 was found to be diphasic or inverted, and we believe this to be an instance in which an inverted P_3 was rendered upright by digitalis.

Case 10.—J. P., aged 40, No. 327. Clinical diagnosis: chronic myocarditis and chronic valvular disease, luetic and rheumatic in origin; confirmed by necropsy.

Electrocardiograms: Normal mechanism. Occasional premature systoles of ventricular origin. Left ventricular preponderance. The P-R interval measured 0.14 sec. in all three leads. P_3 is inverted or diphasic.

After 80 c.c. of tincture of digitalis had been given P_3 was definitely inverted. This inversion was not influenced by vagus pressure, by deep breathing, or by the administration of 2 mg. of atropin. There was no sinus escape after atropin though there was a slight shortening of the P-R interval by 0.03 sec. This observation was repeated and confirmed three days after stopping the digitalis (Fig. 10).

The last records taken seventeen days after digitalis had been discontinued showed P_3 still inverted.

Summary: This case is believed to illustrate an inverted P-wave in Lead III, occurring in a pathologic myocardium, which is not subject to vagus control and is not influenced by digitalis or by atropin.

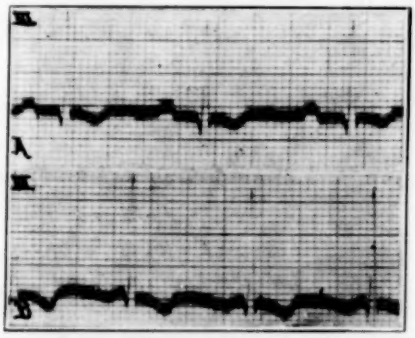

Fig. 9.—Case 9. Lead III. A, after 85 c.c. of digitalis, P_3 upright. Note the broad P-wave. P-R interval 0.22 sec. B, seven days after "B," and ten days after last digitalis, P_3 inverted. P-R interval 0.11 sec. Note the sharp negative P-wave.

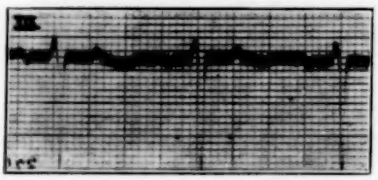

Fig. 10.—Case 10. Lead III. P-R interval 0.14 sec. in all three leads. P_3 permanently inverted.

Case 11.—P. B., aged 34, No. 334. Clinical diagnosis: chronic myocarditis, mitral insufficiency with a moderate grade of decompensation.

Electrocardiograms: Normal mechanism. P_3 definitely inverted. The P-R interval measures 0.17 in Leads I and II. In Lead III with inverted P the P-Q interval measures 0.08 sec. This record was taken after 8 c.c. of digitalis had been given (Fig. 11, A).

After 62 c.c. of tincture of digitalis had been given P_3 was definitely upright. The P-R interval in Leads I and II then measured 0.18. In Lead III the P-Q interval measures 0.17 sec. (Fig. 11, B).

Digitalis was continued until 98 c.c. of the tincture had been given. A marked sinus arrhythmia developed. P_3 remained upright. Six days after

discontinuing the digitalis P_3 is diphasic or upright (Fig. 11, C). Twenty-four hours later, P_3 was inverted. Following the administration of 2 mg. of atropin it became upright in twenty minutes (Fig. 11, D and E).

Two weeks after the last digitalis had been given the P-wave in Lead III showed a spontaneous change from an inverted to an upright P_3 (Fig. 12, F).

Later on P_3 though still inverted became upright during pressure on the right vagus (Fig. 12, G).

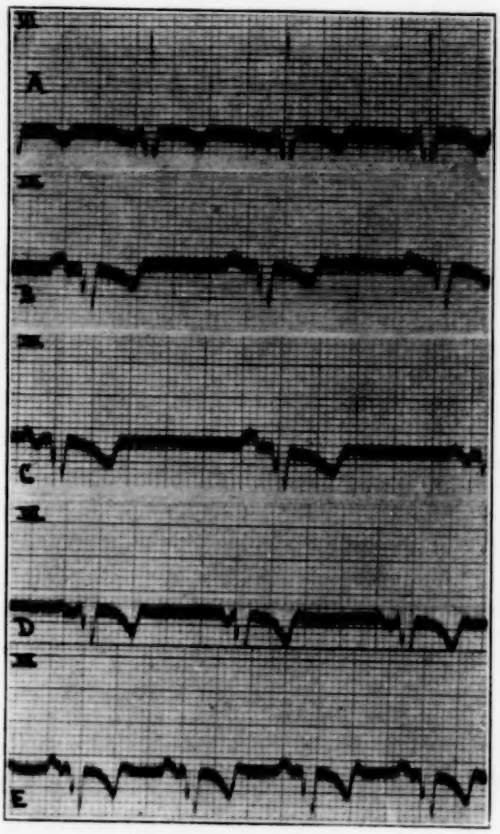

Fig. 11.—Case 11. Lead III. A, after 8 c.c. of digitalis. P-R interval 0.08 sec. P_3 inverted. B, after 62 c.c. of digitalis, P_3 upright. P-R interval 0.17 sec. C, after 98 c.c. of digitalis, P_3 still diphasic or upright. D, seven days after the last digitalis (twenty-four hours later than "C"), P_3 inverted again. E, after atropin, P_3 upright.

During deep breathing marked variations occurred. P_3 appearing upright, inverted or diphasic (Fig. 12, H).

Summary: A case illustrating an inverted P_3 with reversion of its negativity following digitalis, atropin, vagus stimulation and deep breathing, and showing also a spontaneous variation in the negativity of P in Lead III.

Case 12.—T. G., aged 45, No. 361. Clinical diagnosis: chronic myocarditis, chronic valvular disease and aortitis.

Electrocardiograms: Normal mechanism. Left ventricular preponderance. T_1 upright, T_2 and T_3 inverted. P_3 inverted and diphasic. The P-R interval measures 0.18 sec. in all three leads (Fig. 13, A).

Twenty minutes after the administration of 2 mg. of atropin P_3 became upright. The wave was then quite broad, and the P-R interval was shortened

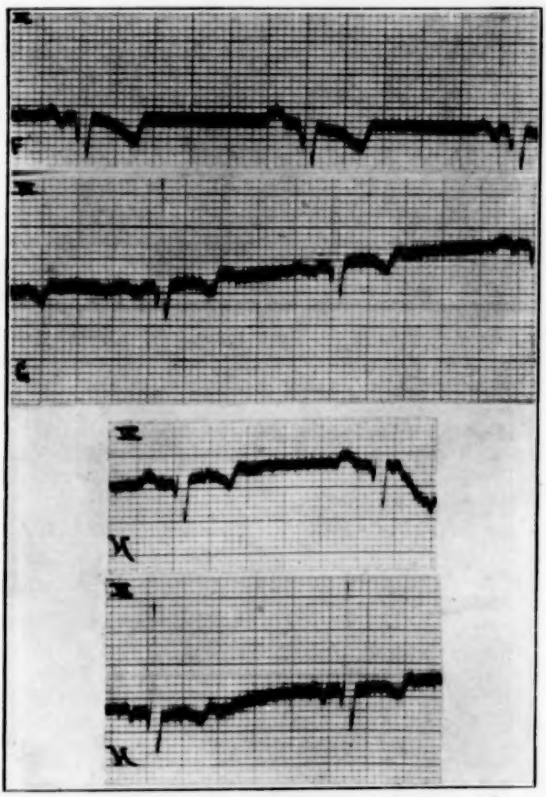

Fig. 12.—Case 11. Lead III, F. Two weeks after digitalis had been discontinued, spontaneous variation in P_3. G, later, P_3 rendered upright by pressure on the right vagus. H, P_3 shows marked variations on deep breathing, upright, inverted and diphasic. P-R interval 0.18, 0.14 and 0.12 sec. This figure cut from a continuous record.

to 0.16 sec. Digitalis was started and the P-wave continued upright during the period of observation (Fig. 13, B).

Summary: A case in which, in the records taken on admission, P_3 was inverted, was promptly rendered upright by 2 mg. of atropin and remained upright during the period of observation throughout which he was taking digitalis.

The foregoing cases may be tabulated as in Table 1.

TABLE 1.—TABULATION OF ELECTROCARDIOGRAMS

Findings	Cases
Positive P_3 inverted by digitalis	1, 2, 5 and 7
Negative P_3 rendered upright by digitalis	3, 6, 9, 11 and 12
Negative P_3 rendered upright by atropin	1, 3, 5, 6, 7, 11 and 12
Negative P_3 persistent, not affected by digitalis, atropin or vagus pressure	4, 8 and 10
P-R interval the same with positive and negative P_3 (after digitalis)	2, 4, 6, 10 and 12
P-R interval with negative P_3 shorter (after digitalis)	3, 5, 8, 9 and 11
Negative P_3 with both normal and ectopic rhythm	8

DISCUSSION OF CASES

By reference to Table 1 it will be seen that in four cases (1, 2, 5, and 7) a normally positive P-wave in Lead III was rendered negative following digitalis. This digitalis effect is marked in Cases 5 and 7 (see corresponding figures). It is also seen that in the presence of a negative P-wave in Lead III this was rendered positive by digitalis in four instances (Cases 3, 6, 11 and 12). See the corresponding figures.

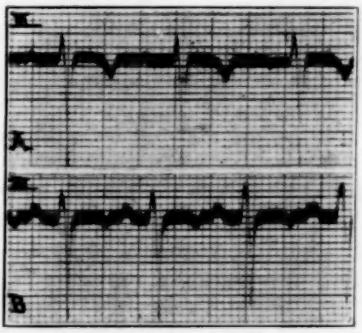

Fig. 13.—Case 12. Lead III. P-R interval 0.18 sec. in all three leads. A, before digitalis P_3 inverted or diphasic. B, after atropin P_3 upright and broad. P-R interval 0.16 sec.

In seven instances with a negative P_3, 2 mg. of atropin promptly reversed this negativity, rendering the P-wave upright.

In three instances the inverted P-wave in Lead III was permanent, being absolutely uninfluenced by digitalis, atropin or vagus pressure (Cases 4, 8 and 10).

The P-R Interval.—Of the eight cases of our series with an originally negative P-wave in Lead III, in four (4, 6, 10 and 12) the P-R interval measured the same in all three leads, and in four (3, 8, 9 and 11) is shorter in the third lead with the negative P_3. In Case 4, of the first group, there was a definite pathologic increase in the conduction time in all leads.

Relationship of the Inverted P_3 to the T-Wave in the Same Lead.—It is obviously difficult to tabulate the relationship of the inverted P-wave in Leal III to the T-wave in the same lead, inasmuch as digitalis was given in every case, and in several instances the P-wave showed a great variability in its negativity, notably Case 8. In the records taken on admission or at the time the inversion of P_3 was first noted, this relationship was as shown in Table 2.

TABLE 2.—Relationship of Inverted P_3 to T-Wave

P_3	T_3	Cases
Negative	Positive	1, 4, 5, 6, 10
Negative	Negative	2, 3, 7, 8, 9, 11, 12*

*P_3 in Case 12, Figure 12, was more often diphasic.

Thus it will be seen from Table 2 that the constancy of the relationship is about equally divided between the presence of a negative P_3 and T_3 and a negative P_3 with a positive T_3.

The Inversion of P_3.—In four of the cases cited the inversion of the P-wave in Lead III was definitely due to the effect of digitalis, and we believe that this inversion is brought about by a change in the muscle balance affecting the electrical negativity in this lead analogous to the alterations causing an inversion of T, and we attribute the corresponding reversal, also seen in four instances, in the presence of a negative P_3 to the same action. That this negativity of the P-wave is also under the influence of the vagi is evident from the reversal that occurred following atropin; though this reversal does not correspond with the effect of atropin on the T-wave made negative by digitalis (Cohn[12]). We consider that this difference may be due to the influence of the digitalis on the volume of atrial muscle mass involved.

In addition to the four instances of a negative P_3 following digitalis there remain seven cases in which a negative P_3 became positive following atropin (Cases 1, 3, 5, 6, 7, 11 and 12). One of these, in which P_3 was first negative, became positive under digitalis and then reverted again, becoming negative seven days after the digitalis had been discontinued; there was a reversal of the invert P both after atropin (Fig. 11, *d* and *e*) and following pressure on the right vagus (Fig. 11, *g*), a paradoxic reaction the essential nature of which is not clear. It is true that this case showed a remarkable spontaneous variation in the negativity of P_3 that was also influenced by deep breathing. We believe that this case illustrates a definite change in the location of the pacemaker in this lead, attributable to vagus influence, with which the greatly shortened conduction time in the presence of the inverted P_3 is consistent.

Of greater interest are the three cases (4, 8 and 10) which showed a persistent negative P-wave in Lead III uninfluenced by digitalis,

atropin, vagal pressure or deep breathing. One of these (8) had a markedly shortened conduction time, 0.12 sec., one (10) a shorter conduction time after atropin, 0.11 sec., and one (4), with a pathologic increase in the P-R interval, a conduction time the same in all three leads, 0.25 sec.

Of these, Case 8 is perhaps the most instructive, as it offers an opportunity to compare the normal rhythm in all three leads with that in the presence of atrial extra systoles, the negative P-wave in Lead III persisting during the normal mechanism and in the presence of the ectopic stimulus (Fig. 8, *a*). With the extra systole the conduction time measures the same in all three leads, 0.12 sec., and in Lead III it remains constant at this figure during the normal rhythm and with the extra systole.

In Lead II we are dealing with an ectopic focus as the origin of the extra systole. In Lead III, considering the extra systole alone, the same conclusion is justifiable, but what shall be said for the inverted P_3 present constantly in this lead in the absence of the extra systole? We believe that the inverted P_3 represents a change of location for the pacemaker in this lead which, in response to the early ectopic impulse, gives rise to an exaggerated negativity (Fig. 8, *a*).

Assuming a demonstrable shortening of the conduction time, together with an inverted P_3, as evidence in favor of the view that there is a definite change in the location of the pacemaker in Lead III, four cases would fulfill this requirement (3, 8, 9 and 11), though two cases of our series (4 and 10) had permanently negative P-waves in Lead III, one of these, however, (4) associated with a definite pathologic increase in conduction time in all leads.

In his paper, previously referred to, Wilson[9] has recorded the abrupt onset, during deep breathing, of an ectopic rhythm originating in the A-V node associated with a definite sudden shortening of the P-R interval seen in Lead II. At no time have we been fortunate enough to catch any change in the location of the pacemaker, attributable to vagal influences or digitalis other than in Lead III.

The Diphasic P-Waves.—The presence of a P-wave essentially diphasic, such as is so well illustrated by Figure 13, and is also so often seen following vagal stimulation, deep breathing, or during digitalis administration, can only mean that there is a great variability in the electrical negativity of the excitation wave in the atrial wall in Lead III, dependent on digitalis effect or vagal tone and influenced possibly by the peculiar relationship of this derivation to the course of the excitation wave in the atrial wall.

It is, of course, possible that these diphasic curves though seen only in one lead (III) may represent an interference with the normal course of the excitation wave for this derivation and in this sense may

be looked on as evidence of pathologic change. There is some evidence in favor of this view in the alteration sometimes seen under digitalis in the typical notched or broadened P-waves present in all leads in some instances of mitral stenosis (Fig. 9 *a* and *b*). For a discussion of the literature up to 1914, see Kahn's[14] monograph.

We believe that we may divide our series of inverted P-waves, seen in Lead III, into two distinct groups; one in which there may be a variation in the site of the pacemaker in its relation to Lead III, conspicuously under the influence of the vagi and digitalis, and a second group in which the relationship of the pacemaker to Lead III is such that a constantly negative P_3 is present utterly uninfluenced by atropin, vagal pressure or digitalis, due possibly to a change of the muscle balance altering the relation of the pacemaker to the axis for this derivation, or to the anatomic distribution of the vagal fibers.

Group I may be looked on as falling into the first and second class described by Wilson as migration of the pacemaker within the s-a node, its immediate neighborhood, or to the a-v node, while Group II, on theoretical grounds, may be considered as a distinct group, though there are difficulties in the way of a too arbitrary division.

CONCLUSIONS

1. The administration of digitalis may lead to an alteration in the negativity of the P-wave in Lead III of the human electrocardiogram.

2. Three instances of the presence of a persistently inverted P-wave, in Lead III, uninfluenced by vagus pressure, atropin, digitalis or deep breathing are recorded.

3. Excepting in the presence of a permanently negative P_3, the electrical negativity of the inverted P-waves in Lead III is reversed by atropin.

4. Additional evidence is cited showing the effect of the vagi on a change in the location of the pacemaker in Lead III.

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14. Kahn, R. H.: Ergebn. d. Physiol., **14**:1, 1914.

EPIDEMIC CEREBROSPINAL MENINGITIS AS OBSERVED AT GENERAL HOSPITAL NO. 6, FORT McPHERSON, GA., WINTER OF 1917 AND 1918*

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AND
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This report includes cases of epidemic cerebrospinal meningitis at General Hospital No. 6, Fort McPherson, Georgia, from Oct. 1, 1917, to May 1, 1918, a period of seven months. Ten patients were treated and the diagnosis was confirmed in every case by the presence of the meningococcus in the spinal fluid.

Methods Employed in Care of Meningitis Cases. — Meningitis patients were isolated in single rooms. Clothing, bed clothes, dishes, bedpans and urinals were sterilized. Throat cultures were taken from convalescent patients every four days until three negative cultures were obtained, and from physicians, nurses and attendants, every four days during their contact with patients. If a positive culture was obtained in a patient he was treated with a spray of dichloramin-T in chlorcosane. Physicians, nurses and attendants received this spray routinely every four hours.

Prophylactic Measures. — The following prophylactic measures were employed immediately on the diagnosis of meningitis being made: All contacts were isolated until negative throat cultures were reported. Any person having a positive culture was immediately isolated until three negative cultures, four days apart, were obtained. The throat was sprayed several times a day with dichloramin-T in chlorcosane. For the six hours preceding a throat culture the spray was not used.

Case 5 of this series illustrates the way in which contacts were followed up. The patient belonged to a hospital unit stationed at Fort McPherson. The entire unit of twelve officers and fifty men were immediately quarantined in their barracks and throat cultures taken. One officer, having left in the interval, was located and ordered to report to the department laboratory of the city in which he was;

* Submitted for publication Oct. 9, 1918.

a telegraphic report being sent by the department pathologist. One carrier was found in this unit, and immediately isolated until three negative cultures were obtained.

Physicians, nurses and attendants wore caps, gowns and masks when entering the patient's room. Physicians and nurses were not isolated when off duty, but attendants, who were not sufficiently trained in taking proper precautions, were isolated.

Our method of dealing with cases on reception at the hospital will be considered later.

Because of the marked variations of severity, symptoms and course presented by our cases, a brief description of each case is necessary before drawing our conclusions.

REPORT OF CASES

Case 1.—The patient came by ambulance from Atlanta. He said that less than twenty-four hours before admission he had had a chill, with nausea, vomiting and headache and a temperature of 104 F. On admission he complained of pain in the chest, cough and fever; the cheeks were flushed. He was admitted as a case of lobar pneumonia.

Examination of the lungs was negative. Blood examination, next day: red blood corpuscles, 4,556,000; white blood corpuscles, 7,000; hemoglobin, 90 per cent.; differential: polymorphonuclears, 82 per cent.; for malaria, negative. His temperature, which was 104.6 on admission (pulse 100, respiration 28), in a few hours dropped to subnormal and remained there for four days. On the fifth day it went to 102.2; white blood cells, 23,800; 90 per cent. polynuclears. The next day, white blood cells 29,800. On the sixth day (November 30) he showed slight stiffness of the neck and a faintly positive Kernig. Lumbar puncture was done; spinal fluid appeared perfectly clear; unfortunately the tube was broken in transmission to the laboratory. Another lumbar puncture was made the next day (December 1); fluid cloudy; 20 c.c. of antimeningococcus serum were administered at once. The laboratory report showed "globulin, double plus; cell count 7,500; smear, very few gram-negative diplococci, some of which were intracellular; culture, hay bacillus (contamination)." From this time on the patient had fever, either intermittent or remittent. At times there was slight delirium. He complained a great deal of headache and morphin was necessary to control it. He was given in all, eleven intraspinous treatments; total, 232 c.c. of serum.

December 10, patient much better; temperature normal. December 11, temperature 102.6; he complained of severe headache and urticaria. In spite of the probability of this being due to the serum, we felt that the continued administration of serum was indicated. Serum was therefore given for the next two days and then discontinued as temperature returned to normal inside of twenty-four hours and the headache likewise disappeared. The urticaria persisted for about three or four days. The patient then made an uneventful recovery and after a month's leave of absence was returned to duty, Jan. 30, 1918.

Case 2.—The patient complained of general pains all over the body, especially in neck and back. Temperature 101; pulse 110; respirations 26. On examination, his neck was somewhat rigid and attempts to elicit the Kernig sign produced slight pain in the back.

Lumbar puncture: fluid cloudy with decreased pressure, and when 12 c.c. were removed the patient complained of such excruciating headache that withdrawal of spinal fluid was stopped and 17 c.c. of serum administered. The introduction of the serum immediately stopped the headache.

REPORT ON SPINAL FLUID

Date	Globulin	Cell Count	Smear	Culture
12/1	++	7,500	Polys., 87%; lymphs., 13%; very few gram-neg. intracellular diplococci	Hay bacillus (contaminated)
12/2	+	.....	.....	Colloidal gold 0-0-0-1-2-3-1-0-0-0
12/3	++	930	Polys., 65%; monos., 35%; occasional gram-neg. diplococci (intracellular)	Negative
12/4	.....	.....	Cells disintegrated; no micro-organisms found	B. subtilis
12/5	.....	.....	.....	Wassermann anticomplementary
12/6	.....	.....	.....	Colloidal gold 0-0-1-2-3-2-2-1-0-1
12/7	++	4,000	Polys., 80%; monos., 14%; numerous gram-neg. intracellular diplococci	Gram-neg. diplococci; no agglutination with polyvalent serum (antimeningitis)
12/8	.....	1,400	.....	Negative
12/9	++	5,700	Polys., 80%; monos., 14%; no micro-organisms	Negative
12/10	++	3,100	Polys., 74%; lymph., 26%	
12/11	+++	760	Polys., 82%; monos., 18%; no micro-organisms	
12/12	+	480	Polys., 18%; monos., 82%; no bacteria	Negative; colloidal gold, 5-5-5-3-2-2-2-1-1-1

REPORT ON INTRASPINOUS INJECTION OF SERUM

Date	Serum Given Intraspinously, C.c.	Fluid Withdrawn, C.c.	Date	Serum Given Intraspinously, C.c.	Fluid Withdrawn, C.c.
12/1/17	22	25	12/ 7/17	20	30
12/2/17	30	30	12/ 8/17	20	30
12/3/17	20	30	12/ 9/17	20	30
12/4/17	20	30	12/10/17	20	30
12/5/17	20	30	12/11/17	30	30
12/6/17	20	30	Total	232	325

The patient was given six intraspinous injections, a total of 115 c.c. At no time was the patient in bad condition or suffering severely. He made an uneventful recovery.

On the eighth day, herpes labialis appeared. On the thirteenth day, serum sickness occurred, with urticaria, but no rise in temperature.

CASE 3.—The patient (Pvt.) was admitted Dec. 15, 1917, with "German measles." December 22 apparently well. December 23, was taken with vomiting and headache, and soon became delirious; opisthotonos present and Kernig positive; lumbar puncture: fluid cloudy; 18 c.c. of antimeningococcus serum administered; nine doses of serum, once daily; total 168 c.c. administered. The patient made an uneventful recovery. On the third day a profuse herpes labialis appeared. Serum sickness occurred December 29, the seventh day,

a fine punctiform, erythematous rash appearing on the face, chest and back, which itched slightly; no headache, pains in joints, or fever. The fever was remittent and irregular, but not intermittent.

Case 4.—The patient (Pvt.) was admitted at 6:30 a. m., Feb. 16, 1918, delirious and struggling. Three men were required to hold him; delirium so profound that he could not be aroused. The only history which could be obtained was that he had been taken with a violet headache at 2 a. m. the same day, and rapidly grew delirious. Temperature was 104, pulse 88, respirations 24. Physical examination was negative. There was no neck rigidity. Kernig was negative. Lumbar puncture was done at 9 a. m.; fluid cloudy; under some pressure; 20 c.c. of antimeningococcus serum administered. Patient grew weaker, and at 1 p. m. died suddenly. The spinal fluid showed globulin quadruple plus; cell count 8,000; smear 95 per cent. polys., monos., 5 per cent.; cells studded with gram-negative diplococci; culture showed meningococcus of intermediate Type 10. Necropsy showed characteristic lesions of the disease.

Report on Spinal Fluid

Date	Globulin	Cell Count	Smear	Culture
1/10	++++	8,000 (estimated)	Many very large gram-negative intracellular diplococci	Meningococcus; agglutination; para type
1/11	++++	15,000	Polys., 80%; monos., 11%; no meningococci seen	No growth
1/12	++	5,000	Polys., 95%; monos., 5%.....	Negative
1/13	++	980	No micro-organisms seen.....	Negative
1/14	++	520		
1/15	++	300	Polys., 40%; monos., 60%; no bacteria	Negative

Report on Intraspinous Injection of Antimeningococcic Serum

Date	Serum Given Intraspinously, C.c.	Fluid Withdrawn, C.c.	Date	Serum Given Intraspinously, C.c.	Fluid Withdrawn, C.c.
1/10	17	12	1/14	20	25
1/11	20	20	1/15	20	20
1/12	18	25			
1/13	18	25	Total	113	127

Case 5.—Patient admitted Jan. 25, 1918; diagnosis, "suspected meningitis." On admission he was delirious; temperature 104. During the afternoon he complained of pains all over the body, especially back of head and neck. He worked until 6 p. m., and at 9 p. m. was in delirious condition; orthotonos, but no opisthotonos; Kernig negative. Lumbar puncture: fluid cloudy; 20 c.c. antimeningococcus serum was administered; treatment continued for three days; delirium disappeared, and the patent became quiet and rational. Temperature ranged from 98.6 to 100, and it was thought that he was beginning to convalesce. The next day his temperature rose, he became delirious and there was marked opisthotonos. One intraspinous treatment was given daily for four days, during which time the patient grew steadily worse. His temperature increased and delirium became profound. He was so restless that it was found necessary to alternate morphin, ¼ grain, and chloral, 10 grains,

sodium bromid, 20 grains, every two hours. Intraspinous treatments were increased to two a day. On the eleventh day of the disease an intravenous treatment of 50 c.c. of serum was given. The immediate effect was a rise in temperature. Six days later a second intravenous treatment was given, and four more the next four days. During all this time the two intraspinous treatments were given daily. The patient would always have a chill within an hour after treatment, with a rise of temperature to about 104. During this time he gradually grew better. The patient received treatments every day for twenty-two days; thirty-three intravenous treatments were given, a total of 675 c.c. of serum, and six intravenous injections, a total of 295 c.c., or a grand total of 970 c.c. of serum. Serum sickness occurred the tenth day after treatment was stopped, and the thirty-second day of the disease. The temperature had been normal for eight days. Serum sickness manifested itself by severe pains in the knees, most pronounced in the left knee, and by a temperature of 104.4.

REPORT ON SPINAL FLUID

Date	Globulin	Cell Count	Smear	Culture
12/23	++++	Disintegrated	Few gram-neg. biscuit-shaped diplococci; some intracellular	No growth
12/24	.....	5,900	Polys., 92%; monos., 8%	
12/25	.....	8,000		
12/26	++	1,700	Polys., 72%; monos., 28%; occasional gram-neg. extracellular diplococci	No growth
12/27	+	750	Polys., 55%; monos., 45%; no bacteria seen	No growth
12/28	+	60	Few disintegrated cells; no organisms.....	No growth
12/29	+	30	.....	No growth
12/31	+	200	.....	Streptococcus, gram-neg.

REPORT ON INTRASPINOUS INJECTION OF SERUM

Date	Serum Given Intraspinously, C.c.	Fluid Withdrawn, C.c.	Date	Serum Given Intraspinously, C.c.	Fluid Withdrawn, C.c.
12/23	18	20	12/28	20	25
12/24	18	22	12/29	20	25
12/25	20	25	12/30	20	25
12/26	17	10	12/31	15	10
12/27	20	25			

Convalescence was very protracted and the patient is still (November 1) in the hospital, but is able to be up and around, though there is back and leg weakness. This postmeningitis asthenia, with spasticity of the legs, has been a feature lasting many weeks after the acute stage and deserves a special study and report.

CASE 6.—Patient (Pvt.) admitted Feb. 21, 1918, in a profound delirium of very acute onset; that is, less than twenty-four hours, and concerning which no history was obtainable. On admission he could not be aroused, struggled constantly, and had to be restrained. Temperature 100.2, pulse 54, respirations 20. Physical examination was negative; no neck rigidity and no Kernig;

lumbar puncture, fluid cloudy; 20 c.c. of serum administered; 20 c.c. intraspinously again administered within six hours of first dose; and 60 c.c. intravenously and two intraspinous treatments for next two days. His delirium had almost cleared up by this time and he was much improved. After one more intravenous and one more intraspinous treatment, the treatments were discontinued, although his temperature was above 102 for two days after the serum was discontinued. The patient made an uneventful recovery. Kidneys showed red blood corpuscles and hyaline, granular and blood casts. He had to be catheterized. On the ninth day, an erythematous rash appeared all over the body, followed by urticaria. There was no fever, headache or pain in joints.

Case 7.—Patient (Pvt.) stepped on nail Feb. 14, 1918, making a superficial puncture on dorsum of left foot. Wound dressed and 15,000 antitetanic serum administered. He was kept in the post hospital. Three days later he had convulsions. Further history not obtainable. Thirty days later he was transferred to General Hospital No. 6, March 16, 1918, with a diagnosis of "(1) concussion of the brain or probable fracture of the skull, accidental; (2) meningitis traumatic; (3) pneumonia, lobar, left upper." The diagnosis on admission was "insanity, followng traumatism, acute." History obtained from paternal uncle: "Father is a drunkard; one maternal aunt had epilepsy; three brothers and one sister are nervous, and patient was always considered feebleminded."

Physical examination on admission showed that the patient was very weak and emaciated; beginning bed sore on right side; eyes protruding, movements free, pupils irregular, oval in outline, central and react sluggishly to light; some increase of intra-ocular tension; tongue dry and coated; knee jerks and ankle jerks markedly exaggerated; no Kernig; no Babinski; abdominal, cremasteric, biceps and triceps reflexes normal; heart, lungs, and abdomen negative. Mental examination: in bed; semiconfused; answers only after questions are repeated several times. Answers are fairly coherent; at times he is very noisy; speech is rambling, and he has acute hallucinoses; he wets and soils himself; lumbar puncture two days after admission; laboratory report on spinal fluid as follows: Wassermann, weakly positive at 0.5 c.c.; globulin double plus; cell count 180; colloidal gold 0-0-0-0-0-0-0-0-0-0-. Roentgenogram of heart, lungs and gallbladder negative. Urine showed a trace of albumin and many casts. Red blood cells, 4,800,000; white blood cells, 13,400; blood culture sterile.

The patient was also examined by the chiefs of the medical and surgical services and the head of the eye service. The eyegrounds were reported negative. The case was regarded as syphilitic meningitis or brain tumor. The patient's temperature was normal.

While in the hospital the patient gradually grew weaker and became greatly emaciated. Persistent vomiting soon developed and followed the taking of food. The temperature remained normal.

Examination April 18, 1918, thirty-three days after admission revealed the following: heart sounds very weak; pulse 116; left patellar reflex normal; right slightly decreased; neck not as flexible as one would expect from a semicomatose patient, though not markedly rigid; well-marked *taché*. Lungs negative. The possibility of a tuberculous meningitis was also considered, and it was planned to examine the spinal fluid for tubercle bacilli, but before this was done the patient died, after being under our care thirty-seven days and in the post hospital before coming here thirty days.

Necropsy showed the ventricles of the brain greatly distended with a semipurulent fluid in which the meningococcus was present. (Internal hydrocephalus, bilateral); meningitis (meningococcus.) The spinal canal was

Report on Spinal Fluid

Date	Cell Count	Globulin	Smear	Culture
1/25	5,000	++++	Many pus cells; gram-neg. intracellular diplococci	Gram-pos. bacillus; probably contam.
1/26	6,000	.....	Few atypical gram-neg. diplococci	
1/27	1,800	.....	Polys., 90%; monos., 10%; no organisms seen	Negative
1/28	2,100	.....	No bacteria	
1/29				
1/30	700	+	No organisms found.....	Negative
1/31	3,800	++	Few extracellular gram-neg. diplococci....	Negative
2/ 1	1,800	++	No organisms seen.....	Negative
2/ 2	1,100	+	Polys., 70%; monos., 30%; no organisms seen	Negative
2/ 5	820	+	No organisms seen.....	Negative
2/ 6	280	+	No organisms seen.....	Negative
2/ 6	over 1,000	.....	No organisms seen	
2/ 7	330	+	Polys., 85%; monos., 15%; no organisms	Negative
2/ 8	170	+++	Many gram-neg. cocci resembling meningococci	Negative
2 /9	1,560	++	No organisms found.....	Staphylococcus albus (Strepto.)
2/10	1,600	++++	No organisms found.....	B. subtilis
2/12	720	+++	No organisms seen.....	B. subtilis
2/14	70	++++	Cells disintegrated; no organisms seen....	Negative

Blood culture, Feb. 11, 1918, sterile.
Blood count, Feb. 15, 1918, red blood cells, 4,270,000; white blood cells, 1,700; polymorphonuclears, 86 per cent.; mononuclears, 14 per cent.

Report on Intraspinous and Intravenous Injection of Serum

Date	Serum Given Intraspinously, C.c.	Fluid Withdrawn, C.c.	Serum Given Intravenously, C.c.	Date	Serum Given Intraspinously, C.c.	Fluid Withdrawn, C.c.	Serum Given Intravenously, C.c.
1/25	20	17		2/ 8	20	50	
1/26	20	30		2/ 8	20	60	
1/27	20	25		2/ 9	20	55	
1/28	20	10		2/ 9	20	60	
1/29	20	8		2/10	20	46	
1/30	20	25		2/10	20	45	40
1/31	20	40		2/11	30	60	
2/ 1	20	38		2/11	25	50	50
2/ 2	20	60		2/12	20	60	
2/ 3	20	45		2/12	20	60	50
2/ 3	20	60		2/13	20	60	
2/ 4	20	45		2/13	20	60	45
2/ 4	20	67	50	2/14	20	40	
2/ 5	20	60		2/14	20	60	60
2/ 6	20	70		2/15	20	60	
2/ 6	20	70			675	1,706	295
2/ 7	20	70			295		
2/ 7	20	70		Total serum given.....	970		

occluded so that the meningeal fluid did not freely enter the spinal canal. Puncture of the cisterna magnum should have been done had the possibility of this occlusion occurred to us.

REPORT ON SPINAL FLUID

Date	Globulin	Cell Count	Smear	Culture
2/21	.....	.....	R. B. C. pus, and some gram-neg. bacilli; no meningococci observed	
2/22	++++	29,000	Many pus cells; gram-neg. intracellular diplococci	Meningococcus — normal agglutinates: 1:400 with normal antiserum; 1:100 with intermediate antiserum; no agglutination with para antiserum; 1:200 with polyvalent antiserum

REPORT ON INTRASPINOUS AND INTRAVENOUS ADMINISTRATION OF SERUM

Date	Serum Given Intraspinously, C.c.	Fluid Withdrawn, C.c.	Serum Given Intravenously, C.c.
2/21	20 25	30 40	60
2/22	20 20	50 15	
2/23	20 20	35 12	
2/24	20	3	55
Total	145	185	115

CASE 8.—Patient was admitted April 18, 1918, from war prison barracks, with a diagnosis of suspected spinal meningitis. He was semidelirious; complained of severe headache, pain in neck and back and vomiting. There was marked opisthotonos. The temperature was 97.6 F., pulse 76, respirations 20. Lumbar puncture clear, under normal pressure. The clinical signs being so marked, 20 c.c. of antimeningococcus serum were given. Laboratory report: spinal fluid, globulin negative; cell count 50; smear negative; culture meningococcus.

The patient was given two intraspinous treatments daily for three days, and then one daily for four days. It was necessary to chloroform him for all of his treatment as he struggled so violently.

At the end of this time it was felt that he was not making satisfactory progress. There was a profound delirium, weak, irregular pulse, and stimulation was necessary for the heart. The temperature was 103.8 and the patient complained incessantly of excruciating pains in the head. The next day the patient was given two intraspinous treatments and one intravenous treatment of 50 c.c. He had a chill and temperature rose to 104.8 and urticaria appeared. The next morning the temperature was normal and remained practically normal all day. All serum treatment was discontinued and patient made an uneventful recovery, the temperature never being more than 1 degree above normal.

REPORT ON SPINAL FLUID

Date	Globulin	Cell Count	Smear	Culture
4/19	Neg.	50	Negative	Meningococcus
4/19	++	2,850	Pus and some partially autolyzed organism, probably meningococci	
4/20	++	1,725	Some pus cells; no organisms	Negative
4/21	++	2,200	Not done	Not done
4/22	++	1,300	Not done	Not done
4/22	+++	500	Not done	Not done
4/25	++	3,400	Not done	

April 27: White blood cells, 11,100; polymorphonuclears, 82 per cent.; mononuclears, 18 per cent.

REPORT ON INTRASPINOUS AND INTRAVENOUS ADMINISTRATION OF SERUM

Date	Serum Given Intraspinously, C.c.	Fluid Withdrawn, C.c.	Serum Given Intravenously, C.c.
4/19	20	30	
4/19	20	30	
4/20	20	30	
4/20	20	20	
4/21	20	50	
4/21	20	50	
4/22	30	30	
4/23	..	50	
4/24	26	40	
4/25	24	60	
4/26	30	40	
4/26	30	40	
4/26	..	..	50
Total	274	470	50

Blood count April 27, 1918: white blood cells 11,000, polymorphonuclears 82 per cent., mononuclears 18 per cent. June 28, 1918, this patient had recurrence of meningitis which ran a course similar to the initial attack and from which he recovered.

CASE 9.—The patient (Pvt. J.), who was admitted from Camp Gordon with a diagnosis of "fever, type undetermined," said that while on a hike two days before his left arm and side began to feel numb, with pain in shoulders and back of neck. On admission he seemed in fairly good condition; complained of pain in back and soreness in the back of neck. There was also a "catchy" pain over the heart at times. Physical examination showed a few râles at base of left lung, with bronchial breathing over left upper lobe.

There was slight tenderness over left side of abdomen. The temperature was 100.4, pulse 80, respirations 20. First diagnosis, "influenza."

April 20, 1918, thirteen days later, the temperature was 104, pulse 104, respirations 28, with nausea, vomiting, rigidity and tenderness over right side of abdomen. He was seen by the surgical service as a possible case of appendicitis. Blood showed white blood corpuscles 32,800. Examination for malaria was negative. Headache developed, with pain and stiffness of neck and slight Kernig.

April 22, the temperature was 102.8, pulse 86, respirations 28. Lumbar puncture under chloroform secured a cloudy fluid. Twenty c.c. of antimeningococcus serum were given. The next day two intraspinous treatments were given, and then one daily for three days. Four days after the last serum and eight days after first serum was given, the patient broke out with urticaria. He made an uneventful recovery.

REPORT ON SPINAL FLUID

Date	Globulin	Cell Count	Smear	Culture
4/22	++	6,100	Pus and a few extracellular gram-negative diplococci	Negative
4/23	++	2,700	Not done.....	Not done

REPORT ON INTRASPINOUS INJECTION OF SERUM

Date	Serum Given Intraspinously, C.c.	Fluid Withdrawn, C.c.	Date	Serum Given Intraspinously, C.c.	Fluid Withdrawn, C.c.
4/22	20	50	4/25	20	40
4/23	20	60	4/26	30	40
4/23	20	50			
4/24	20	25	Total	130	265

CASE 10.—The patient (Pvt.) who was admitted April 9, 1918, with a diagnosis of "influenza," for two days prior to admission complained of fever, headache and pain across the abdomen, extending to back; similar complaint on admission. Physical examination was negative, except for a slight pharyngitis. Temperature on admission, 102.2; normal in four days, when patient appeared to be convalescing. April 22, thirteen days after admission, he had a chill after supper. The temperature rose to 104, pulse 86, respirations 20. His temperature next morning was 100.6. He complained of headache, pain in back of neck and generalized pain in abdomen. Opisthotonos was present and Kernig faintly positive, yet his answers were so contradictory, and he was so frightened when examined that one felt doubtful about the signs. Lumbar puncture fluid was purulent. The laboratory report showed pus cells and thousands of meningococci. Twenty c.c. of antimeningococcus serum were administered. At this time the temperature was 104, pulse 160, and respirations 36, the two latter probably due to fright. The next day the temperature was subnormal all day. One intravenous treatment of 50 c.c. was given, and intraspinous treatments, one of 20 c.c., and some of 40 c.c. Two intraspinous treatments were given daily for two days more. The temperature gradually increased up to 101. Treatment was then omitted for three

days, when one intraspinous injection of 15 c.c. was given. April 30, the patient had a chill, with rise of temperature to 103.6, but during the next three days it returned to normal, and the patient made an uneventful recovery.

April 28, he complained of pain in the left ankle; May 1, pain in both ankles; May 2, orchitis, left. There was no rash or rise of temperature.

REPORT ON SPINAL FLUID

Date	Globulin	Cell Count	Smear	Culture
4/23	++	400	Pus and thousands of meningococci	Meningococcus

REPORT ON INTRASPINOUS AND INTRAVENOUS ADMINISTRATION OF SERUM

Date	Serum Given Intraspinously, C.c.	Fluid Withdrawn, C.c.	Serum Given Intravenously, C.c.
4/23	20	40	
4/24	20	50	
4/24	40	60	
4/24	..	..	50
4/25	16	35	
4/25	20	50	
4/26	20	50	
4/26	30	40	
4/30	15	40	
Total	181	378	50

SUMMARY

Our experience and conclusions may be summed up as follows:

Ten cases of epidemic cerebrospinal meningitis were treated. Two men died, one an extremely fulminating case, who lived less than twelve hours after the onset and who received an intraspinous treatmet of 2 c.c of antimeningococcus serum; the other, an unrecognized and untreated case in which the man lived sixty-seven days, and in which diagnosis was either a syphilitic or tuberculous meningitis, and in which necropsy revealed a walled-off meningococcus infection of the brain.

The physical signs at the onset; that is, when first examined at the hospital, were as follows:

Kernig sign was present in 5 cases, or 50 per cent.; opisthotonos was present in 3 cases, or 30 per cent.; orthotonos was present in two cases, or 20 per cent.; delirium was present in 6 cases, or 60 per cent.; headache was present in 8 cases, or 80 per cent. (in the

other two cases the history was not obtainable); fever was present in eight cases, or 80 per cent. (in four of these cases the temperature was 104 or more).

The pulse was slow in comparison to the temperature, only one case showing the pulse above 103. Respirations were slightly increased. In 5 it was 20, and the other 5 ranged from 22 to 30. Vomiting was present in 6 cases, or 60 per cent. Lumbar puncture showed a cloudy fluid in 7 cases, or 70 per cent. In 3 cases, or 30 per cent., it was clear. A chill occurred in 3 cases, or 30 per cent.

During the course of the disease, the following findings were recorded: Serum sickness occurred in every treated patient except two, and one of these lived only four hours after his first treatment. The other patient was a negro, and he developed pain in ankles and testicles, and there was no rash. Of the six cases in which opisthotonos was absent at the onset, it developed later in two. Orthotonos was a common feature.

Of the five cases in which the Kernig sign was absent at the onset, it developed in two. Herpes labialis occurred in three cases, or 30 per cent. Purpura and rash, except that from serum sickness, was absent in all cases. The "spotted" rash described as one of the features of this disease did not occur in any of our cases. Three patients, or 30 per cent., required catheterizing. All patients ran a febrile temperature.

CONCLUSION

In conclusion, we would like to emphasize the following points: The cases here reported showed no uniformity of symptoms or signs. Marked variations of symptoms was the rule. Those symptoms and signs which in our cases appeared with the greatest uniformity were as follows: headache 100 per cent., fever 80 per cent., delirium 60 per cent., vomiting 60 per cent., Kernig 50 per cent., opisthotonos 30 per cent., orthotonos 20 per cent.; but no cases presented the hemorrhagic spinal "spotted" rash. In connection with the latter we have questioned whether the early administration of serum prevented the meningococcus from producing widespread toxic effects. Certainly, the prompt improvement following administration of serum supports such a theory, as indicated by the majority of our cases. If the "spotted" rash heretofore described as characteristic of this disease is due to hemolysis from an associated hemolytic streptococcus, one would be disposed to conclude that its absence in those patients treated early was due to the prevention of toxemia. If the petechial rash were due to septic emboli, these too would be associated with a similar toxemia checked by early serum treatment. Two of our patients showed no signs except fever and delirium.

The early diagnosis of this disease is of the greatest importance, as danger of infection of others is thereby lessened, and by early treatment the patient has the best chance of recovery. In many cases, early diagnosis is only possible by lumbar puncture and examination of the spinal fluid. Therefore, all doubtful cases should receive lumbar puncture, which, if properly done, is a comparatively simple, and a relatively safe procedure. Cases of fever and delirium with no other physical signs should have this done. When performing a lumbar puncture, *one should have everything ready to administer serum. If the spinal fluid is cloudy, or if clear with physical signs of meningeal involvement, give* 20 or 30 c.c. of antimeningococcus serum.

Not only is early treatment important, but intensive treatment should be started at once. Two intraspinal treatments of from 20 to 30 c.c. should be given every twenty-four hours. The intraspinous treatments should be given thus for the first few days, and decreased as the patient improves clinically.

As to the use of intravenous treatment, while we do not feel justified in drawing any conclusions, our feeling has been that all patients who come in with marked toxic symptoms, and all who are doing badly, should be thus treated. Fifty or 60 c.c. are given intravenously as often as once in every twenty-four hours, following the method of Cole. Very commonly a chill, followed by a rise of temperature to 103, 104, or even 105, occurs, but this is often followed by a drop to normal or even subnormal, and should cause no alarm. Herrick* reported the successful use of intravenous meningococcus serum at Camp Jackson. Herrick's report brought out valuable discussion to which the reader is referred.

Case 8 indicates that the intravenous treatment will at times bring about favorable results when the intraspinous method seems to fail.

As to when all serum therapy should be discontinued, it is very difficult to decide. In this connection the temperature is of practically no value as a guide. Normal or subnormal temperature may be present at the onset or during the first few days, while fever may be due to the effect of the serum. The two most reliable guides are the *spinal fluid* and the *general condition of the patient*. Treatment should not be discontinued until the spinal fluid is clear and free from meningococci, and not until the patient is clearly in much better condition, free from delirium and toxic signs. Serum sickness, which was present in practically all of our cases, may cause headache and fever and be mistaken for actual symptoms of the disease itself. The presence of a rash, usually urticaria, and pain in the joints, will often serve to differentiate the two.

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* Proceedings of Assn. Am. Phys., May, 1918, to be published.

A safe way is to omit serum treatment for one day, then for two days, and if the patient continues to improve, discontinue it entirely.

One thing to bear in mind is that serum is the only method of treatment, and that if properly administered it cannot cause any permanent symptoms. Serum sickness is not a contra-indication to further treatment. Therefore, give serum as soon, as frequently, and in as large doses as possible.

The method of serum administration we used was as follows: The patient lies on his side, with his back at the edge of the bed. The knees and hips are flexed as far as possible, and the back bowed out. Opisthotonos increased the difficulty of successful puncture. Often ¼ grain of morphin, one-half hour before treatment would relax and quiet the patient. In some cases it was necessary to use chloroform. The operator should wear gloves to protect both himself and the patient. The amount of fluid that should be removed varies not only in individual cases but in the same case from day to day. "With the spinal fluid under pressure I (Bowman) have twice removed 70 c.c. in twenty-four hours. In some cases with decreased pressure, I (Bowman) have been unable to remove more than 12 c.c. because of the patient's complaining of such excruciating headache." In these latter cases, injection of the serum immediately caused a disappearance of the headache. Usually from 20 to 30 c.c. of serum was given intraspinously, 40 c.c. being the largest dose. If the serum would not flow freely, slight pressure from a syringe was used to force it in.

For the extreme delirium, morphin and chloral may be used freely. When one realizes the energy a restless, delirious patient uses up every twenty-four hours, and the long-drawn-out character of the disease in some cases, it seems wise to save the patient's energy as well as to make him comfortable by the use of these drugs.

The diet must not be neglected. It is common to order "liquid diet" for febrile and delirious patients. The high caloric diet as in typhoid should also be applied to meningitis. We found that one overactive, delirious patient who was twisting and turning in bed night and day and talking incessantly, was using twice the energy of the average well man, and was receiving less than 1,000 calories a day. After a conference with our dietitian, Miss de Garmo, a special diet was arranged for all our patients, which, of course, varied a great deal in individual cases, but which averaged from 2,000 to 2,500 calories. Attention to or neglect of this may turn the scale in desperately ill patients.

Bladder distention should be watched for in all delirious patients. In one of our cases, incontinence with retention occurred, and was

Data of Authors' Cases

	Case									
	1	2	3	4	5	6	7	8	9	10
Kernig at onset	0 developed later	+	+	0	0 developed later	0	0	++	+	+
Opisthotonos at onset	0 developed later	0	+	0	0 developed later	0	0	++	+	+
Orthotonos	0	+	..	0	+	0	?			
Temperature at onset	104.6	100.0	101.0	104.0	104.0	100.2	99.0	97.6	100.4	104.0
Pulse at onset	100	102	116	88	80	54	80	76	80	86
Respiration at onset	28	22	30	24	24	20	20	20	20	20
Delirium at onset	0 later	0	+	+	+	+	+	+	0	?
Headache at onset	+	+	+	+	+	?	?	+	+	+
Vomiting at onset	+	0	+	0	0	0	+	+	+	+
Serum sickness	+	+	+	0	+	+	0	+	+	?
Appearance of fluid at first puncture	Clear	Cloudy	Cloudy	Cloudy	Cloudy	Cloudy	Clear	Clear	Cloudy	Cloudy
First puncture—										
Cell count	7,500	8,000	?	8,000	5,000	Pus	180	50	6,100	400
Globulin	++	++++	++++	++++	++++	++++	++	0	++	++
Smear	Menin. (87% Poly.)	Many paramenin.	Menin. +	Menin. +	Menin. 0	Menin. 0	Not done	Menin. 0	Menin. +	Menin. +
Culture	Hay bac.	.....	No growth	Menin. +	Menin. 0	Menin. 0	Not done	Menin. +	Menin. 0	Menin. +
Amount serum given, C.c.	232	114	168	20	675 S + 295 V = 980	145 S + 115 V = 260	0	274 S + 50 V = 324	130	181 S + 50 V = 231
Number of treatments	11	6	9	1	33 S + 6 V = 39	7 S + 2 V = 9	0	13 S + 1 V = 14	6	8 S + 1 V = 9
Outcome	Cured	Cured	Cured	Died	Cured	Cured	Died	Cured	Cured	Cured
Herpes	+	+	0	0	0	0	0	0	0	0
Chill at onset	+	Chilliness	0	?	0	?	0	0	0	+

only relieved by catheterization. Attendants and nurses should be cautioned to report slight incontinence of urine, as it may be an important index of retention. The urine should be carefully measured. In delirious cases, retention of urine may greatly add to the restlessness of the patient.

An accident which occasionally occurs is the *breaking of the needle* in the spinal column. This occurred in one of the earlier cases treated at this hospital, and has occurred at other military hospitals. In our case a subsequent operation successfully removed the fragment of the needle and at no time were there any ill effects. This risk is now overcome by using a needle made of a metal which is *bendable* but not breakable.

It has been found helpful to place on the wall *in consecutive order* the temperature charts, record of serum and blood examination and the daily record of calories taken and the amounts of serum given. This is a simple clinical point, but when the fight with the disease is at its height, the map of the operation offers a quick and graphic way of determining how the fight is going and enables the physician to direct his forces.

FURTHER STUDIES CONCERNING THE ESSENTIAL NATURE OF ANTITRYPTIC ACTIVITY OF NORMAL SERUM AND THE PHYSIOLOGIC FUNCTION OF PANCREATIC FERMENTS *

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A. REVIEW OF THE LITERATURE ON THE ANTITRYPTIC ACTION OF NORMAL SERUM

We have records of a great number of experimental observations on the antitryptic power of normal serum. The significance of this antitryptic power, however, has not yet been determined.

The power that normal serum possesses for preventing the action of trypsin, so far as I have been able to learn, was first definitely noticed by Hahn,[1] in 1897, who said that this action disappeared on heating after at from 65 to 70 C. Fermi and Pernossi,[2] in 1894, had noticed that trypsin rapidly disappeared after injection into the animal body, and that it was destroyed by contact with the tissues in vitro. On the significance of this power, Landsteiner,[3] in 1900, stated that the antiaction of serum against trypsin was intimately connected with the albumin fraction, after coming down between half and full saturation of the serum with ammonium sulphate. Oppenheimer and Aron,[4] in 1903, also observed that the resistance of serum to trypsin digestion depends on the configuration of the protein molecules; but, on the other hand, Glaessner,[5] in 1903, contradicted Landsteiner's observation, and concluded that it was associated with the euglobulin, that is, the fraction precipitated by one-third saturation with ammonium sulphate. In 1904, however, Cathcart[6] proved Landsteiner's observation, and also that globulin does not possess antitryptic action, that absolute specificity does not exist and that this antiaction is effected by heating for 30 minutes at 60 C. in the presence of alkali, and at about 70 C. in its absence. Delezenne and Pozarski,[7] in 1903, found

* Submitted for publication Oct. 1, 1918.

* From the Laoratory of Preventive Medicine, University of Chicago.

1. Hahn: Berl. klin. Wchnschr., **34**: 1897.
2. Fermi and Pernossi: Ztschr. f. Hyg., **18**: 1894.
3. Landsteiner: Centralbl. f. Bakt., **27,** Nos. 10 and 11, Abt. 1, 1900.
4. Oppenheimer and Aron: Hofmeisters' Beitr. z. chem. Phys. u. Path., **4**: 1903.
5. Glaessner: Hofmeisters' Beitr. z. chem. Phys. u. Path., **4**: 1903.
6. Cathcart: Jour. Physiol., **31**: 1904.
7. Delezenne and Pozarski: Compt. rend. Soc. de biol., **55**: 1903.

that the serum preserved with chloroform soon lost its antitryptic action. Bayliss,[8] in 1904, and Abderhalden and Gigon,[9] in 1907 found that some of the products of tryptic activity possess the property of inhibiting the action of the ferment, the free amino-acids more than the polypeptids. Bayliss and Starling,[10] in 1905, observed that the anti-enzyme seems only to inhibit enzyme action and not to destroy the enzyme itself. In 1906, Wells[11] considered why it was that certain body tissues were not digested by their own enzymes but by the enzymes of one another. He goes on to state that in some way the growth of anti-enzymes in the cells and tissue fluids are greatly impeded by the serum. Wiens,[12] in 1907, believed that the antiferment in serum was a true antibody, but that the antigen is a ferment liberated by the polymorphonuclear cells. In 1908, Jochmann and Kantorowicz[13] found that antitrypsin is thermolabile and loses its action by heating for thirty minutes at 60 C. Bergmann and Bamberg[14] found that the antitrypsin in normal serum is constant. Eisner,[15] in the same year, studied the inhibiting action of serum against various ferments and concluded that it possessed a special affinity for trypsin, but Weil[16] disproved his observation in 1910. Mayer,[17] in 1909, obtained almost the same result as that of Bayliss and Starling in 1905, thus opposing the view of Delezenne,[18] in 1901, who stated that the antitryptic action of the blood is due to an antikinase. He believed that the antibody acted on the trypsin. Döblin,[19] however, in 1909, stated that the antitryptic action of normal serum is not a true immune antibody, but is colloid and thermolabile. In the same year, Schwartz[20] found that the antitryptic activity of serum is due to the lipoids of serum which partially inactivated the serum by extracting it with ether; and the serum can be reactivated by the addition of lecithin. On the contrary, Cobliner,[21] in 1910, assumed that lipoids are not active agents. Dried serums extracted with ether, chloroform or petroleum ether do not lose their antitryptic activity. Rosenthal,[22] in this year, believed that the antitryptic action of normal serum is due to protein cleavage products, and its increase in carcinoma

8. Bayliss and Starling: Arch. d. sc. biol., 1904, Suppl. 9.
9. Abderhalden and Gigon: Ztschr. f. physiol. Chem., **53**: 1907.
10. Bayliss and Starling: J. Physiol., **32**: 1905.
11. Wells: J. M. Res., **10**: 1906.
12. Wiens: München. med. Wchnschr., **54**: 1907.
13. Jochmann and Kantorowicz: Ztschr. f. klin. Med., **66**: 1908.
14. Bergmann and Bamberg: Berl. klin. Wchnschr., 1908, No. 30.
15. Eisner: Ztschr. f. Immunitätsf., Orig., 1, 1908-1909.
16. Weil: Am. J. M. Sc., **139**: 1910.
17. Mayer: Biochem. Ztschr., **23**: 1909.
18. Delezenne: Compt. rend. Soc. de biol., **53**: 1901.
19. Döblin: Ztschr. f. Immunitätsf., **4**: 1909.
20. Schwartz: Wien. klin. Wchnschr., **22**: 1909.
21. Cobliner: Biochem. Ztschr., **25**: 1910.
22. Rosenthal: Folia serolog., **6**: 1910.

and other diseases with cachexia can be thus explained; he also found that this activity decreases during fastings, and increases during digestion. These facts were proved by Franz and Jarisch[23] in 1912. Meyer,[24] in 1911, does not believe that protein cleavage products are the inhibiting agents. He believes that antitrypsin is a true antibody, and that the ferment of tissue cells acts as antigen. In this year,

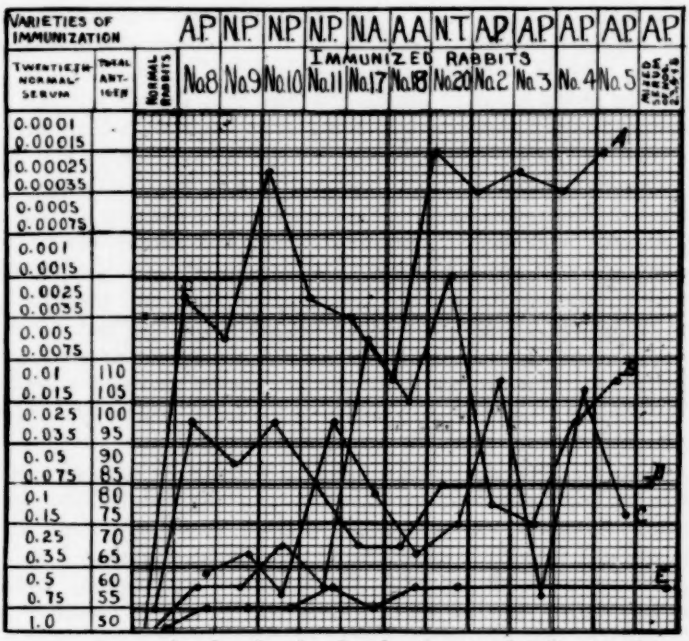

Chart showing the relation between the production of antibodies and the antitryptic action of serum. A. P. = alcoholic pancreatin; N. P. = native pancreatin; N. A. = native amylopsin; A. A. = alcoholic amylopsin; N. T. = native trypsin; A line = precipitation; B line = complement deviation; C line = total amount of antigens; D line = complete digestion of fibrin; E line = partial digestion of fibrin.

Weiberg and Ruenstein[25] found that ultraviolet rays destroyed the antitryptic substance in human serum. Rubenstein[26] also observed that the antitryptic power disappeared by heating at 70 C. In 1912, Abderhalden[27] found that during pregnancy there developed in the

23. Franz and Jarisch: Wien. klin. Wchnschr., **25**: 1912.
24. Meyer: Folia serolog., **7**: 1911.
25. Weiberg and Rubenstein: Compt. rend. Soc. de biol., **71**: 1911.
26. Rubinstein: Compt. rend. Soc. de biol., **71**: 1911.
27. Abderhalden: München. med. Wchnschr., **59**: 1912.

blood specific enzymes for digesting placenta proteins. The blood of a pregnant woman shows constantly an increased antitryptic power. In 1914, Bronfenbrenner[28] observed that any normal serum placed in contact with "sensitized" placenta acquired the same property. Therefore, it might be surmisable that the Abderhalden reaction would be composed of two phases: the one specific for the sensitization of placenta, the other nonspecific for the autodigestion of the serum as a result of the presence of sensitized placenta; and he[29] also said that the specificity of the Abderhalden reaction depends not as Abderhalden believed, on the presence of specific enzymes, but on the presence in the blood of pregnant women of a specific antibody that combines with placenta antigen and thus sets free the only proteolytic enzymes which is always present in the normal serum. In 1913, Kirchheim[30] concluded that the antiferment merely prolongs the action of the trypsin and does not destroy it, confirming Bayliss and Starling's experiments. He also found chloroform reduced the inhibiting action of the serum as Delezenne and Pozarski's experiments proved. Sugimoto,[31] in 1913, observed that there was a decrease in the antitryptic strength of serum after the serum had been extracted with ether and benzol. He concluded that the lipoids were the active constituents. Confirming Schwartz, he believed also that a complete extraction of fat and the dissociation of the lipoid-protein combinations will cause a removal of the ferment inhibiting action. In this year we have a critical discussion on the significance of antitryptic action of normal serum by Kämmerer,[32] Kämmerer and Aubry,[33] and Rosenthal.[34] Kämmerer contradicted Rosenthal's theory and asserted that the globulin fraction is inhibited like the albumin fraction. This antitryptic action is affected at 56 C. Rosenthal was opposed to Kämmerer's theory, but in 1914, Jobling and Petersen[35] observed that the ferment-inhibiting substances of the serum are lipoids corresponding to Schwartz's and Sugimoto's observation, and that they are in fat solvents, and lose their ferment inhibiting action when heated with serum at 70 C., similar to Rubenstein's observation.

On the antitrypsin in pathologic serum, Brieger and Trebing,[36] in 1908, found that it increases in carcinoma and sarcoma, and this was proved by Bergmann and Meyer.[37] Bergmann and Bamberg[14]

28. Bronfenbrenner: Proc. Soc. Biol. and Med., **12**: 1914, No. 1.
29. Bronfenbrenner: Biochem. Bull., **4**: 1915.
30. Kircheim: Arch. f. exper. Path. u. Pharmakol., **73**: 1913.
31. Sugimoto: Arch. f. exper. Path. u. Pharmakol., **74**: 1913.
32. Kämmerer: München. med. Wchnschr., **60**: 1913.
33. Kämmerer and Aubry: Biochem. Ztschr., **48**: 1913.
34. Rosenthal: München. med. Wchnschr., **60**: 1913.
35. Jobling and Petersen: J. Exper. Med., **19**: 1914.
36. Brieger and Trebing: Berl. klin. Wchnschr., 1908, Nos. 22, 29 and 45.
37. Bergmann and Meyer: Berl. klin. Wchnschr., 1908, Nos. 37 and 45.

found antitrypsin not only in carcinoma and sarcoma, but present in acute infections and chronic diseases such as pneumonia, typhoid fever, tuberculosis, syphilis, chronic anemia, basedow, amebic dysentery, pancreas necrosis of men, and various sicknesses.

On the significance of antitryptic action of normal serum, therefore, we have at present no definite agreement. This important subject stimulated my interest and I have followed it up in the experiments to be described.

B. ON THE INHIBITION OF NORMAL SERUM AGAINST PANCREATIC DIGESTION

EXPERIMENT 1.—*The Inhibiting Action of Normal Ox, Sheep, Rabbit and Guinea-Pig Serum against Fibrin Digestion by Pancreatin.*—For this examination the following materials were used: (*a*) Half-normal serum of 5 oxen, 5 sheep, 8 rabbits and 6 guinea-pigs; (*b*) one c.c. of a 1 per cent. pancreatin salt solution filtered through a Berkefeld filter added to every tube, which contained half-normal serum; (*c*) carmin-stained oxfibrin about the size of an apple seed.

TABLE 1.—INHIBITING POWER AGAINST PANCREATIN DIGESTION OF NORMAL RABBIT SERUM

Results in 24 hours at 38 C. with 1 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Rabbit 1	Rabbit 2	Rabbit 3	Rabbit 4	Rabbit 5	Rabbit 6	Rabbit 7	Rabbit 8
0.35	0	0	±	0	0	±	0	0
0.25	++	++	+++	+++	+++	+++	++	+++
0.15	+++	++++	++++	++++	++++	++++	+++	++++
0.1	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
0.075	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.

In this and following tables 0 denotes a negative for fibrin digestion; ± = trace (very slight digestion); + = slight digestion (partial); ++ = medium digestion; +++ = marked digestion; Comp. = complete digestion; ++++ = almost complete digestion.

TABLE 2.—THE INHIBITING POWER AGAINST PANCREATIN DIGESTION OF NORMAL OX SERUM

Results in 24 hours at 38 C. with 1 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Ox 1	Ox 2	Ox 3	Ox 4	Ox 5
0.35	0	0	0	0	0
0.25	0	0	0	0	0
0.15	++	+++	++	+++	+++
0.1	++++	++++	++++	+++	++++
0.075	Comp.	Comp.	Comp.	Comp.	Comp.

TABLE 3.—The Inhibiting Power against Pancreatin Digestion of Normal Sheep Serum

Results in 24 hours at 38 C. with 1 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Sheep 1	Sheep 2	Sheep 3	Sheep 4	Sheep 5
0.35	0	0	0	0	0
0.25	0	0	0	0	0
0.15	+++	+++	+++	++	+++
0.1	++++	Comp.	++++	+++	Comp.
0.075	Comp.	Comp.	Comp.	Comp.	Comp.

TABLE 4.—The Inhibiting Power against Pancreatin Digestion of Normal Guinea-Pig Serum

Results in 24 hours at 38 C. with 1 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Pig 1	Pig 2	Pig 3	Pig 4	Pig 5	Pig 6
0.35	0	0	0	0	0	0
0.25	0	0	0	0	0	0
0.15	0	0	0	0	0	0
0.1	++	+++	++	++	+++	++
0.075	+++	+++	++++	+++	++++	+++
0.05	Comp.	++++	Comp.	Comp.	Comp.	++++
0.035	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.

The results in Tables 1 to 4, inclusive, show that normal animal serum has an inhibiting power against pancreatin digestion of oxfibrin, but the extent of this inhibiting power differs appreciably in the different animals. In my experiment 0.35 c.c. of half-normal rabbit serum inhibited completely fibrin digestion with 1 c.c. of a 1 per cent. pancreatin, 0.25 c.c. of a ox and sheep half serum and 0.15 c.c. of a guinea-pig half serum.

On the neutralization of the inhibiting power of normal serum against trypsin, Achalme and Stevenin,[38] in 1911, stated that 0.01 or 0.015 c.c. of trypsin neutralized 0.006 c.c. of human serum, 0.015 c.c. of rabbit serum and 0.01 of guinea-pig serum. My experiments with regard to the amount of pancreatin necessary for the neutralization of the inhibiting power of normal rabbit, ox, sheep and guinea-pig serum against pancreatin differ very much from those of Achalme and Stevenin in their results, as shown in the foregoing tables: 0.35 c.c.

38. Achalme and Stevenin: Compt. rend. Soc. de biol., 1911, **70,** No. 12.

of rabbit half serum, 0.25 c.c. of ox and sheep half serum and 0.15 c.c. of guinea-pig half serum were neutralized completely by 1 c.c. of a 1 per cent. pancreatin. Therefore, 0.1 c.c. of rabbit serum is necessary to neutralize 0.006 of pancreatin, 0.1 c.c. of ox and sheep serum neutralizes 0.008 of pancreatin, and 0.1 c.c. of guinea-pig serum neutralizes 0.013 of pancreatin. The inhibiting power of guinea-pig serum, therefore, is the strongest among the serums, such as ox, sheep and rabbit serum, the rabbit serum being the weakest.

EXPERIMENT 2.—*Effect of Heat on the Inhibition of Normal Ox, Sheep, Rabbit and Guinea-Pig Serum against Fibrin Digestion by Pancreatin.*—The technic for fibrin digestion by pancreatin in this experiment was just the same as in Experiment 1, but the quantity of 1 per cent. pancreatin used was 0.35 c.c. to each tube.

TABLE 5.—THE EFFECT OF HEAT ON THE INHIBITION OF NORMAL RABBIT SERUM AGAINST PANCREATIC DIGESTION

Results in 24 hours at 38 C. with 0.35 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Unheated Serum	Heated Serum, 56 C. 30′	Heated Serum, 65 C. 30′
1.0	0	0	Comp.
0.75	0	0	Comp.
0.5	0	±	Comp.
0.35	0	++++	Comp.
0.25	0	Comp.	Comp.
0.15	0	Comp.	Comp.
0.1	+	Comp.	Comp.
0.075	Comp.	Comp.	Comp.
0.05	Comp.	Comp.	Comp.

TABLE 6.—THE EFFECT OF HEAT ON THE INHIBITION OF NORMAL OX AND SHEEP SERUM AGAINST PANCREATIC DIGESTION

Results in 24 hours at 38 C. with 0.35 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Unheated Serum	Heated Serum, 56 C. 30′	Heated Serum, 65 C. 30′	Heated Serum, 70 C. 30′
1.0	0	0	0	Comp.
0.75	0	0	0	Comp.
0.5	0	0	0	Comp.
0.35	0	0	+++	Comp.
0.25	0	0	Comp.	Comp.
0.15	0	++	Comp.	Comp.
0.1	0	Comp.	Comp.	Comp.
0.075	+	Comp.	Comp.	Comp.
0.05	+++	Comp.	Comp.	Comp.
0.035	Comp.	Comp.	Comp.	Comp.

TABLE 7.—The Effect of Heat on the Inhibition of Normal Guinea-Pig Serum against Pancreatic Digestion

Results in 24 hours at 38 C. with 1 per cent. pancreatin

Half-Normal Serum, C.c.	Unheated Serum	Heated Serum, 56 C. 30′	Heated Serum, 65 C. 30′
1.0	0	0	+
0.75	0	0	Comp.
0.5	0	0	Comp.
0.35	0	0	Comp.
0.25	0	0	Comp.
0.15	0	0	Comp.
0.1	0	Comp.	Comp.
0.075	0	Comp.	Comp.
0.05	0	Comp.	Comp.
0.035	++++	Comp.	Comp.
0.025	Comp.	Comp.	Comp.

Tables 5, 6 and 7 show that the inhibiting action of normal serum against pancreatin digestion is affected by heating. It was fairly affected by heating for thirty minutes at 56 C., and lost its power at 65 or 70 C., corresponding to the results of Hahn, Cathcart, Rubenstein, Rosenthal and Jobling and Peterson, but not to those of Jochmann-Kantorowicz, Kämmerer, and Kämmerer and Aubry. The extent of the effect of heating, however, differs on the different species of animals, according to the tables; that is, rabbit serum has the weakest resistance against heating compared with ox, sheep, and guinea-pig serum; guinea-pig serum has the strongest resistance to heating; ox and sheep serum are almost equal in this respect and have a stronger resistance than rabbit serum, but weaker than guinea-pig serum. It may be said that the antitryptic substance of normal serum is fairly thermostabile, and also that the quantity of this substance seems to be constant.

C. PRECIPITATION OF NORMAL RABBIT SERUM BY PANCREATIN SOLUTION

According to current literature, we have two views on the essential nature of the antitryptic substance of normal serum, namely, that of a true immune antibody, according to Wiens, Eisner, and Mayer, and of nonspecificity, according to Cathcart, Döblin and Rosenthal. We also have three views of the production of so-called antitrypsin in normal serum. According to Landsteiner the antitryptic action is intimately connected with the albumin fraction, which is approved by Cathcart and Rosenthal. According to Glaessner and Kämmerer

the antitryptic action is associated with globulins. The third view is that the ferment inhibiting substance of the serum are the lipoids, as advocated by Schwartz, Sugimoto, and Jobling and Petersen.

The interesting question as to whether or not the antitryptic substance is a true antibody, and what the source of this substance is, invited my further attention. If this antitryptic substance is a true antibody it must have immune reactions, so that I carried out the following experiment for the determination of immune reactions.

EXPERIMENT 3.—*Determination of Immune Reactions.*—For this experiment the serums of forty-one normal rabbits were employed; for the precipitation, trypsin (Central Scientific Co.), pancreatin (Parke, Davis & Co.), and amylopsin (Digestive Ferments Co.) were used as antigen. The antigens were employed in 1 per cent. solution (dissolved in 0.85 per cent. sodium chlorid solution), filtered through a Berkefeld filter. I obtained four positive results out of a total of forty-one cases, as shown in Table 8.

TABLE 8.—PRECIPITATION OF NORMAL RABBIT SERUM BY TRYPSIN

Dilution of Half-Normal Serum, C.c.	Rabbit A			Rabbit B			Rabbit C			Rabbit D		
	Trypsin	Pancreatin	Amylopsin	Trypsin	Pancreatin	Amylopsin	Trypsin	Pancreatin	Amylopsin	Tryp. sin	Pancreatin	Amylopsin
1.0	+	−	−	+	−	−	++	−	−	+	−	−
0.75	+	−	−	+	−	−	+	−	−	+	−	−
0.5	+	−	−	+	−	−	+	−	−	+	−	−
0.35	±	−	−	−	−	−	±	−	−	±	−	−
0.25	−	−	−	−	−	−	−	−	−	−	−	−

− = negative; + = very slight positive; ± = trace.
41 cases: 37 cases negative; 4 cases positive.

These results show that the anti-enzyme-like substance of normal serum seems to have a special affinity for trypsin, according to Eisner's view, and also the quantity of this so-called antitrypsin is constant.

According to Landsteiner, I treated the four positive serums for fifteen minutes in a half saturation with ammonium sulphate, and tested it again for precipitation. I could not find any precipitation at all. The precipitation of the untreated serum with ammonium sulphate for trypsin should be only a pseudoprecipitation. If, again, the albumin fraction has an important significance in the inhibiting action of serum, the serum of rabbits and guinea-pigs treated with ammonium sulphate might lose the inhibiting action.

With this point in view I examined the serum treated with ammonium sulphate ($(NH_4)_2SO_4$) for the inhibiting action of pancreatin on fibrin digestion, but could find only a very slight decrease, as shown in Tables 9 and 10.

TABLE 9.—Comparison of the Inhibiting Power of Rabbit Serum Treated and Untreated with Ammonium Sulphate against the Fibrin Digestion of Pancreatin

Result in 24 hours at 38 C. with 1 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Rabbit A		Rabbit B		Rabbit C		Rabbit D	
	Untreated	Treated	Untreated	Treated	Untreated	Treated	Untreated	Treated
0.5	0	0	0	0	0	0	0	0
0.35	0	+++	0	Comp.	0	+++	0	++++
0.25	++	Comp.	+++	Comp.	++	Comp.	++	Comp.
0.15	++++	Comp.	Comp.	Comp.	+++	Comp.	+++	Comp.
0.1	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.

Control: 1. $(NH_4)_2SO_4$ (½ Sat.) + pancreatin + fibrin = complete digestion.
2. NaCl (0.85 per cent.) + pancreatin + fibrin = complete digestion.

TABLE 10.—Comparison of the Inhibiting Power of Guinea-Pig Serum Treated and Untreated with Ammonium Sulphate against the Fibrin Digestion of Pancreatin

Result in 24 hours at 38 C. with 1 c.c. of 1 per cent. pancreatin

Half-Normal Serum, C.c.	Untreated	Treated
0.15	0	0
0.1	±	Comp.
0.075	++++	Comp.
0.05	Comp.	Comp.

The results in Tables 9 and 10 show that the so-called antitrypsin of normal serum is not a true antibody as Wiens, Eisner and Mayer believed, but acts like a "pseudo-antiferment," or especially like a "pseudo-antitrypsin" in this instance, and the albumin fraction of serum has not an important significance for the antitryptic action as Landsteiner, Cathcart, Döblin and Rosenthal believed, but it seems to have more or less relation to the antitryptic power of the serum.

D. THE RELATION BETWEEN THE ANTITRYPTIC ACTION OF NORMAL SERUM AND ANTICOMPLEMENT

Believing that a factor of the antitryptic action of normal serum would also be associated with complement, I tried to find out the relation of the antitryptic action to the anticomplement. For this experiment I employed the serums of two rabbits and a normal guinea-pig.

First I examined the inhibiting action of the rabbit serum against the fibrin digestion of pancreatin, the precipitation for guinea-pig serum and the complement fixation; after that I immunized the rabbits

TABLE 11.—Inhibiting Action of the Serum of Rabbits A and B Before and During Immunization with Normal Guinea-Pig Serum

Result in 24 hours at 38 C.

Half-Normal Serum, C.c.*	Before Injection		During Immunization	
	Rabbit A	Rabbit B	Rabbit A	Rabbit B
0.5	0	0	0	0
0.35	0	0	+	++
0.25	++	+	Comp.	Comp.
0.15	+++	+++	Comp.	Comp.
0.1	Comp.	Comp.	Comp.	Comp.

* One c.c. of 1 per cent. pancreatin was aded to each tube, and a small piece of carmin-stained oxfibrin was used as in the first experiment.

TABLE 12.—Precipitation of the Serum of Rabbits A and B Before and During Immunization with Guinea-Pig Serum

Serum, C.c.*	Before Injection		During Immunization	
	Rabbit A	Rabbit B	Rabbit A	Rabbit B
1.0	0	0	++++	+++++
0.5	0	0	+++	++++
0.25	0	0	++	+++
0.1	0	0	+	++
0.05	0	0	+	++
0.025	0	0	+	+
0.01	0	0	0	+
0.005	0	0	0	±

* One c.c. of a 20 times dilution of guinea-pig serum as antigen was used for this examination.

TABLE 13.—Complement Fixation of the Serum of Rabbits A and B Before and During Immunization with Normal Guinea-Pig Serum

Rabbit Serum, C.c.*	Before Injection		During Immunization	
	Rabbit A	Rabbit B	Rabbit A	Rabbit B
1.0	None	None	Complete	Complete
0.5	None	None	Complete	Complete
0.25	None	None	Almost complete	Complete
0.1	None	None	Partial	Almost complete
0.05	None	None	Trace	Partial
0.025	None	None	None (complete hemolysis)	None (complete hemolysis)

* 1. Rabbit serum was inactivated for thirty minutes at 56 C. 2. Complement employed, 0.5 c.c. of a 10 per cent. guinea-pig serum. 3. Five per cent. sheep blood 0.5 c.c. + 0.2 per cent. antisheep serum, 0.5 c.c.

with normal guinea-pig serum and tested the serum again for the inhibiting action against pancreatic digestion, the precipitation for guinea-pig serum and the complement fixation with the immunized rabbit serum. These experiments are as follows:

EXPERIMENT 3.—Protocols of Experiment 3. Rabbit A: Feb. 8, 1918. Body weight, 2,500 gm. Bled and tested with this serum for precipitation for guinea-pig serum, complement fixation, and inhibiting action against fibrin digestion of pancreatin.

After these examinations I injected 5 c.c. of a 10 times dilution of guinea-pig serum (0.1 c.c. of 10 times dilution of guinea-pig serum hemolyzed completely 0.5 c.c. of 5 per cent. sheep red blood corpuscles suspension).

February 9. Body weight, 2,450 gm. Injected 5 c.c.
February 10. Body weight, 2,420 gm. Injected 5 c.c.
February 11. Body weight, 2,420 gm. Injected 10 c.c.
February 13. Body weight, 2,410 gm. Injected 15 c.c.
February 22. Body weight, 2,600 gm. Bled on the ninth day after the last injection and tested for the precipitation of guinea-pig serum, the complement fixation, and the inhibition against the fibrin digestion of pancreatn.

Rabbit B: Feb. 8, 1918. Body weight, 2,450 gm. This case was treated the same as Rabbit A. Injected 5 c.c. (10 guinea-pig serum).

February 9. Weight, 2,400 gm. Injected 5 c.c.
February 10. Weight, 2,400 gm. Injected 5 c.c.
February 11. Weight, 2,350 gm. Injected 10 c.c.
February 13. Weight, 2,350 gm. Injected 12 c.c.
February 22. Weight, 2,200 gm. Bled the ninth day after the last injection and tested for

The results shown in Tables 11, 12 and 13 indicate that the anticomplement to the complement of guinea-pig serum and the "anti-pseudo-antitrypsin" were surely formed in the immunized rabbit serum, and the antitryptic action of the immunized rabbit serum was decreased.

In 1902, Korschun[39] found that antiantilab-ferment was formed in serum by the injection of normal horse serum, which contains an antilab, into normal horse; this observation relates to the chemical reaction. I suppose that the action of the antilab ferment of normal horse serum, decreased by the production of the antiantilab, would also probably be associated with the production of anticomplement, as in my experiments.

E. APPEARANCE OF A TRYPTIC ENZYME IN NORMAL URINE

Enzymes of various kinds have been isolated from normal urine. Among these may be mentioned pepsin (Brücke,[40] Sahli[41]); trypsin (Kühn,[40] Bendersky,[40] Tesulli,[40] Sahli[41]); diastatic ferment (Cohn-

39. Korschun: Hoppe-Seyler's Ztschr. f. physiol. Chem., **36**: 1902.

40. Brücke: Kühn, Bendersky, Tasuli, Cohnheim, Grützner, Holovtschiner, Helwes, Hopkins, Neumeister and Boas: Huppert-Neubauer, Ed. 10, 1908, p. 599.

41. Sahli: Pflüger's Arch. f. d. ges. Physiol., **36**: 1885.

heim[40]), and lab ferment (Grützner,[40] Holovtschiner,[40] Helwes[40]). Among these proteolytic enzymes in normal urine, Hopkins[40] could not prove trypsin, Neumeister[40] pepsin in rabbit urine, and Boas[40] lab ferment at all; and Matthes,[42] in 1903, stated that pepsin appears in normal human and dog urine but not trypsin. Schoenborn,[43] in 1910, stated that pepsin, diastase and rennin all have been found in normal urine, but trypsin is chiefly a trypsinogen, especially abundant after a meat diet.

EXPERIMENT 4.—*Tryptic Enzyme in Normal Urine.*—I wanted to know whether or not a tryptic ferment appears in normal urine and I experimented with the urine of nine normal rabbits. The colorimetric method for the digestion of the carmin-stained oxfibrin was used and the urine was aseptically taken from the bladder and centrifugalized before the examination.

TABLE 14.—TRYPTIC ACTION OF NORMAL RABBIT URINE

Results in 24 hours at 38 C.

Dilution Used,* C.c.	Rabbit 1	Rabbit 2	Rabbit 3	Rabbit 4	Rabbit 5	Rabbit 6	Rabbit 7	Rabbit 8	Rabbit 9
1.0	0	0	0	Comp.	0	0	Comp.	0	0
0.75	0	0	0	Comp.	0	0	Comp.	0	0
0.5	0	0	0	Comp.	0	0	Comp.	0	0
0.35	0	0	0	Comp.	0	0	++	0	0
0.25	0	0	0	0	0	0	+	0	0
0.15	0	0	0	0	0	0	0	0	0
0.1	0	0	0	0	0	0	0	0	0

* The urine was filtered aseptically through Berkefeld filter. A piece about the size of an apple seed of the carmin-stained oxfibrin was added to each tube containing the urine, the contents covered with toluol and incubated for twenty-four hours.

Table 14 shows that a tryptic enzyme may appear in a small amount in normal rabbit urine in a few cases (two in nine cases).

F. THE APPEARANCE OF ANTITRYPSIN IN NORMAL URINE

Döblin,[44] in 1909, found antitrypsin in normal urine (positive results in four of thirty cases) with the casein method, but Müller and Kolaczeck,[45] in 1907, could find no antitrypsin in normal urine. In my experiments I could find no antitrypsin in normal rabbit urine; I therefore made the following experiment:

EXPERIMENT 5.—*Determination of Antitrypsin in Normal Rabbit Urine.*—For this experiment I employed the urine of nine normal rabbits obtained from the bladder and centrifugalized before the examination. I used a 1 per cent.

42. Matthews: Arch. f. exper. Path. u. Pharmakol., **49**: 1903.
43. Schoenborn: Ztschr. f. Biol., **53**: 1910.
44. Döblin: Ztschr. f. Immunitätsf. u. exper. Therap. **4**: 1909.
45. Müller and Kolaczek: München. med. Wchnschr., 1907, No. 8.

trypsin (Central Scientific Co.) in salt solution, filtered through a Berkefeld filter, and for the test for inhibiting action to fibrin digestion I used 0.2 c.c. of a 1 per cent. pancreatin (Parke, Davis & Co.) in salt solution, filtered through Berkefeld filter. I could obtain no positive result for the precipitation of the immune reaction, nor any positive reaction for inhibition against pancreatic digestion. (A piece about the size of an apple seed of carmin-stained oxfibrin in 1 c.c. of urine was completely digested with 0.2 c.c. of a 1 per cent. pancreatin.)

G. THE ESSENTIAL NATURE OF THE ANTITRYPTIC ACTION OF NORMAL SERUM

Considering my foregoing experiments, the essential nature of the anitryptic action of normal serum can not be explained in a simple manner, but it is reasonable to suppose that there are existing non-specific "pseudo-antiferments," especially "pseudo-antitrypsin" in this instance. As a product of the physiologic processes of tissue cells these "pseudo-antiferments" not only inhibit the autodigestion of tissue cells, but also foreign ferments outside of the body.

The increase of the antitryptic power of the serum in malignant diseases such as carcinoma and sarcoma, or acute and chronic diseases such as pneumonia, typhoid fever, tuberculosis, syphilis, chronic anemia, etc., can be explained by the increase of "pseudo-antiferments" in order to prevent the autodigestion of tissue cells or foreign ferments. These "pseudo-antiferments," therefore, are of important significance for the antiferment-like action of serum.

The reason for this opinion is that the essential nature of the antitryptic action is a nonspecific "pseudo-antiferment" and that the antitrypsin-like substance of normal serum is fairly thermostabile, and sometimes takes the place of the "pseudoprecipitation" by trypsin; that the production of antipseudo-antitrypsin, as well as the quantity of antitrypsin-like substance, is constant and the normal serum also has the inhibiting action against enzymes of various kinds as observed by many workers.

As the secondary factors, the albumin fraction and the complement of the serum are associated with it, because the antitryptic action is stronger in the serums of animals which have a strong complement, like guinea-pig serum, and also stronger in the serums which have an abundance of serum albumin, such as ox, sheep, and guinea-pig serums, as well as decreased by the production of anticomplement, and also by the treatement of the serum with ammonium sulphate.

H. THE FATE OF THE ENZYME PANCREATIN INTRODUCED INTO THE BLOOD STREAM OF NORMAL RABBITS

1. *The Fixation of Pancreatin Injected as Antigen.*—The statement is often made in regard to the origin of antibodies that antibodies are formed in the blood itself by the leukocytes or the hemopoietic organs.

Up to a recent time, however, we have no conclusive evidence of that, but Hektoen and Carlson,[46] in 1909, found that the antigens injected intravenously, at least in some animals, are quickly removed from the blood or in some way so changed that the antigenic property is lost, and antibodies are not produced in the blood. The removal or change of the antigen takes place within three to six hours. Antibodies in active immunization are produced outside of the blood stream. According to Luckhardt and Becht's[47] observation in 1911, the production of the antibodies with "immune" tissue, specific antibodies with "immune" spleen were obtained, while "immune" heart muscle, liver, bonemarrow and lymph gland did not give positive results. They concluded that the spleen takes a significant part in the fixation of antigen. Luckhardt and Becht, however, found the production of antibody resulted even in asplenic animals. In 1912, Pettit and Carlson[48] observed that the soluble and insoluble antigens are fixed outside of the blood stream. Recently, Kyes[49] has shown that certain endothelial cells of the liver and spleen are constantly active in phagocyting red blood corpuscles from the circulating blood stream; these he designates as "hemophages." This interesting investigation was trustworthily proved by Cary,[50] Berry and Melick[51] in this laboratory. On the possibility of the activity of these hemophages, Kyes explained that foreign erythrocytes, certain bacteria and some colloids injected into the blood stream are rapidly taken up and digested by the hemophages, so that the hemophages are definitely concerned in antibody production.

Kyes,[52] by his study, in 1916, on the natural resistance of the pigeon to the pneumococcus, has shown that phagocytosis of fixed tissue cells is not only most active in the hemophages of liver and spleen, but exists in the fixed tissue cells of lung, bonemarrow, kidney, pancreas and intestine, although its activity is very weak. Bartlett and Ozaki,[53] in 1917, also stated that *Micrococcus aureus* introduced into the blood stream of dogs is stored up in relatively great numbers in the lung capillaries and is rapidly ingested by morphonuclear leukocytes, but in considerable numbers in wandering cells and fixed cells of the spleen and liver, and also in small numbers, or not at all, in the blood, bonemarrow, kidney, intestinal wall, heart muscle and skeletal muscle. It seems to me that they[54] are surely proving Kyes' observation by

46. Hektoen and Carlson: Tr. Chicago Path. Soc., **8**: 1909, No. 1.
47. Luckhardt and Becht: Tr. Chicago Path. Soc., **8**: 1911, No. 6.
48. Pettit and Carlson: J. Infect. Dis., **10**: 1912, No. 1.
49. Kyes: Internat. Monatschr. f. Anat. u. Physiol., **31**: 1914.
50. Cary: J. Infect. Dis., **17**: 1915, No. 2.
51. Berry and Melick: J. Immunol., **1**: 1916, No. 1.
52. Kyes: J. Infect. Dis., **18**: 1916, No. 3.
53. Bartlett and Ozaki: J. Med. Res., **35**: 1917, No. 3.
54. Bartlett and Ozaki: J. Med. Res., **37**: 1917, No. 1.

their study on phagocytosis in vivo under various conditions, because the bacteria employed by them were phagocyted in great numbers by the fixed tissue cells of liver and spleen.

According to Ozaki,[55] the accumulation of bacteria in the spleen, such as occurs in experimental bacteremia, depends on the vital activity of the cells and the mechanical filtration of bacteria by the spleen, which is not an important factor. The kidney, on the other hand, may be a much more effective filter than the spleen. Recently, Okazaki[56] found by his study on the fate of the starch granules injected into the rabbit's vein that some colloidal substance such as starch was phagocyted by some endothelial cells such as those of lung capillaries and Kuppfer's cells, or some giant cells.

The following experiments on the fate of the pancreatin introduced into the blood stream of rabbits might explain the significant rôle of the physiologic function of tissue cells against foreign colloids, as well as the fixation of antigens by tissue cells.

EXPERIMENT 6.—*Fate of Pancreatin Introduced Into the Blood.*—For this experiment I employed fifty-three rabbits, which were injected with pancreatin intravenously. I also used nine other rabbits for control examinations. The experimental rabbits were killed with chloroform at intervals in order to determine the fate of pancreatin injected as antigen; that is, to find out where the antigen was fixed, or if it was fixed, whether or not it had a timely relation.

With this point in view, seven rabbits were killed thirty minutes after the injection, 10 rabbits at one hour, 7 at one and a half hours, 6 at two hours, 3 at two and a half hours, 2 at three hours, 1 at five hours, 1 at six hours, 1 at twelve hours, 3 at twenty-four hours, 2 at thirty-eight hours, 5 at forty-eight hours, 3 at fifty-four hours, 1 at sixty hours, and 1 at seventy-two hours, and also 9 for control.

As an antigen to be injected, 1 per cent. native pancreatin filtered through a Berkefeld filter and 2 per cent. alcoholic pancreatin were used.

Glycerin extracts of the rabbits' organs, such as bone-marrow, spleen, liver, kidney, suprarenal capsule and lung, were made. The examination was then carried out on the following material:

1. Half-normal serum. 2. Ten per cent. organ glycerin extracts. This latter extract was prepared in the following way: The organs were cut into small pieces with scissors and ground up by mixing with sea sand in a mortar and then extracted with 50 per cent. glycerin solution. This extract, after being kept for twenty-four hours at room temperature, was mixed with a small amount of chloroform to avoid putrefaction, following Salkowski's[57] suggestion. Finally, this extract was filtered through a porcelain fiter.

Method of Examination.—The method of carmin-stained fibrin digestion was employed to obtain an indication of the presence of antigen in three tissue extracts and serum. The tissue extracts and serum were examined in graded dilution with a physiologic sodium chlorid solution to the amount of 2 c.c. in every tube, and a small piece of fibrin the size of an apple seed and the solution covered with toluol and then incubated for twenty-four hours at 38 C. To the fibrin digestion of the tissue extract there was added 1 drop of tenth-normal sodium hydroxid to each tube. During this examination aseptic precautions were observed as far as possible.

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55. Ozaki: J. Med. Res., **36**: 1917, No. 3.
56. Okazaki: The Sei-i-Kwai Med. J. (Tokio), **36**: 1917, No. 10.

By this method the following results were obtained: In 7 rabbits killed thirty minutes after injection the antigen was found in the bonemarrow in 6 cases, in the spleen in 5 cases, in the liver and lung in 2 cases, in the kidney in 1 case and in the suprarenal capsule in 4 cases. In 10 rabbits, killed after one hour, antigen was found in the bonemarrow and liver in 7 cases, in the spleen in 6 cases, in the kidney in 4 cases, in the suprarenal capsule in 5 cases and in the lung tissue in 3 cases; no antigenic reaction was found in 1 of 10 cases. In 7 rabbits, killed after one and a half hours, the antigen was found in the bonemarrow in 5 cases, in the spleen and liver in each of 2 cases, in the kidney in 2 cases, in the suprarenal capsule in 4 cases and in the lung in 1 case. In 6 rabbits, killed after two hours, the antigen was found in the bonemarrow in 4 cases, in the spleen in 3 cases, in the liver in 5 cases, in the kidney and suprarenal capsule in 2 cases, while there was no antigenic reaction in any extract in 1 of 6 cases.

In 3 rabbits, killed at two and a half hours, antigen was found only in the bonemarrow and liver of 1 case each; in 2 rabbits, killed at three hours, in only the bonemarrow, liver and kidney of each case; in 1 rabbit, killed at five hours, antigen was found in the bonemarrow and spleen; in 1 rabbit, killed after six hours, it was found in the bonemarrow, spleen, liver, kidney and suprarenal capsule; in 1 rabbit, killed at twelve hours, it was found in the bonemarrow, spleen, liver and kidneys; in 3 rabbits, killed at twenty-four hours, it was found in the bonemarrow and spleen in each case, in the liver in 1 case, and in the kidney in 2 cases; in 2 rabbits, killed at thirty-eight hours, it was found in the bonemarrow, spleen, kidney and suprarenal capsule of each case, and in the liver in 1 case; in 5 rabbits, killed at forty-eight hours, it was found in the bonemarrow and spleen in each case, and in the liver and kidney in 3 cases; in 3 rabbits, killed at fifty-four hours, 1 rabbit killed at sixty hours, and also 1 at seventy-two hours, no antigenic reaction was found.

Of the antigenic reaction of the serum, it was positive in 6 of 7 animals, which were killed at thirty minutes after injection; in 8 of 10 cases killed at one hour, in 5 of 7 cases killed at one and a half hours, and in 4 of 6 cases killed at two hours, while a negative result was obtained in other cases; also, at the same time, the inhibiting action of the serum against pancreatic digestion was examined in order to determine the presence of the antigen in the serum, concerning which I obtained the following results: the inhibiting action of the serum of rabbits killed within two hours after the injection was markedly decreased compared with that of normal serum, while no decrease of this power was found in cases in which the rabbit was killed after two hours.

As a control, tissue extracts and serum of nine rabbits were carefully examined for pancreatic action, but no positive results were found.

Summarizing these facts, the enzyme, pancreatin, introduced into the blood stream was probably phagocyted by the fixed tissue cells of the body, and seemed to keep its activity during two days, while the antigen in the serum seemed to exist for two hours after the injection, and after that would be phagocyted by fixed tissue cells. The antigen seemed to be markedly phagocyted in the hemopoietic organs within one hour after injection, although it was more or less fixed by other organs.

2. *The Excretion of Pancreatin Injected as Antigen.*—As I have already shown, the urine of some normal rabbits contains a small amount (0.35, or 0.25 in the lowest active dilution) of some tryptic enzyme. In my foregoing experiment it was positive in two of nine rabbits. I carried out the following experiment with a view of finding out whether or not pancreatin introduced into the blood stream is excreted into the urine; if so, how much is excreted.

EXPERIMENT 7.—*Excretion of Pancreatin in Urine.*—For this experiment I employed the urine taken directly from the bladder of fifty rabbits into which I had injected the pancreatin, and also that of nine normal rabbits. This urine was centrifugalized before examination. The method for the pancreatic digestion of the urine was the same as that for serum.

The urines in six of fifty animals injected and seven of the nine normal specimens were negative. The amount of pancreatin excreted in the urine in the remaining forty-four cases is not large as compared with that of normal urine. I assume, therefore, that the pancreatin is phagocyted by the tissue cells. The excreted pancreatin was found in the urine in from thirty minutes to fifty-four hours after the injection.

I. ANTITRYPTIC ACTION OF IMMUNE SERUMS AND TISSUE EXTRACTS WITH PANCREATIC FERMENTS

I wanted to know the relation between the production of antibodies and the antitryptic action of serums and tissue extracts from animals immunized with pancreatic ferments. For this purpose rabbits were immunized to a higher degree with both unmodified and alcohol modified pancreatin, trypsin, and amylopsin, with which I carried out the experiments. The pancreatic ferment solutions employed were made by the following procedure:

a. Unmodified pancreatic ferment solutions. Commercial pancreatin (Parke, Davis & Co.), trypsin (Central Scientific Co.) and amylopsin (Digestive Ferments Co.) in powders were added to physiologic sodium chlorid solution in the amount of 1 per cent. by weight. After repeated shaking the solutions were filtered through hard-pressed filters and finally through Berkefeld candles. The resulting filtrate was clear and sterile.

TABLE 15.—The Antitryptic Action of Tissue Extracts of Immunized Rabbits. Results in Twenty-Four Hours at 38 C.

10% Tissue Extract, C.c.	Varieties of Immunization												Control, Eight Normal Rabbits
	Pancreatin	Pancreatin	Pancreatin	Pancreatin	Pancreatin	Pancreatin	Pancreatin	Pancreatin	Pancreatin	Amylopsin	Amylopsin	Trypsin	
	Rabbit 2	Rabbit 3	Rabbit 4	Rabbit 5	Rabbit 6	Rabbit 8	Rabbit 9	Rabbit 10	Rabbit 11	Rabbit 17	Rabbit 18	Rabbit 20	
Bone Marrow													
1.0	+	0	0	0	0	0	0	0	+++	+	+	+++	Comp.
0.75	Comp.	+	0	0	+	Comp.	0	0	Comp.	+	++	++++	Comp.
0.5	Comp.	Comp.	+++	0	+	Comp.	0	0	Comp.	++	+++	++++	Comp.
0.35	Comp.	Comp.	++++	Comp.	+	Comp.	+	++	Comp.	++++	Comp.	++++	Comp.
0.25	Comp.	Comp.	Comp.	Comp.	+	Comp.	+	+++	Comp.	Comp.	Comp.	Comp.	Comp.
0.15	Comp.	Comp.	Comp.	Comp.	+	Comp.	+	+++	Comp.	Comp.	Comp.	Comp.	Comp.
Spleen													
1.0	+	0	0	0	0	+	0	0	Comp.	±	+++	++++	Comp.
0.75	+	+	0	0	0	+	0	0	Comp.	++	+++	Comp.	Comp.
0.5	+	+	+	±	±	Comp.	0	0	Comp.	Comp.	Comp.	Comp.	Comp.
0.35	+	+++	+++	Comp.	+	Comp.	Comp.	±	Comp.	Comp.	Comp.	Comp.	Comp.
0.25	Comp.	Comp.	Comp.	Comp.	+	Comp.	Comp.	++	Comp.	Comp.	Comp.	Comp.	Comp.
0.15	Comp.	Comp.	Comp.	Comp.	+	Comp.	+	+++	Comp.	Comp.	Comp.	Comp.	Comp.
Liver													
1.0	0	0	0	0	0	0	0	0	+	+	+	0	Comp.
0.75	0	0	0	0	0	0	0	0	+	+	++	0	Comp.
0.5	±	0	±	0	0	+	0	0	+	+	++	+	Comp.
0.35	+	+	+	+	0	+	0	0	+	++	+++	++	Comp.
0.25	++	+	+	+	0	Comp.	++	0	+++	+++	++++	+++	Comp.
0.15	++	+	+	+	+	Comp.	++	+	+++	++++	Comp.	+++	Comp.
Suprarenal Capsule													
1.0	+	Comp.	+++	Comp.	Comp.	Comp.	0	++	Comp.	Comp.	Comp.	Comp.	Comp.
0.75	Comp.	Comp.	+++	Comp.	Comp.	Comp.	0	++++	Comp.	Comp.	Comp.	Comp.	Comp.
0.5	Comp.	Comp.	+++	Comp.	Comp.	Comp.	0	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
0.35	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	+	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
0.25	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	++	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
0.15	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.	++	Comp.	Comp.	Comp.	Comp.	Comp.	Comp.
Kidney													
1.0	0	0	0	0	0	0	0	0	++++	+	++	+	Comp.
0.75	±	±	0	0	0	+	0	0	++++	+	Comp.	+	Comp.
0.5	+	+	0	0	0	Comp.	0	0	Comp.	Comp.	Comp.	++	Comp.
0.35	+	+	+	0	++	Comp.	0	0	Comp.	Comp.	Comp.	++	Comp.
0.25	++	±	++	+	++	Comp.	+	+	Comp.	Comp.	Comp.	Comp.	Comp.
0.15	++	+++	+++	+	++	Comp.	+++	++	Comp.	Comp.	Comp.	Comp.	Comp.

Total amount of tissue extract in each tube made, 2 c.c. with 0.85 per cent. NaCl.
Control test for glycerin: 1 c.c. of a 50 per cent. glycerin + 1 c.c. of 0.85 per cent. NaCl + 0.2 c.c. of 1 per cent. pancreatin + fibrin = complete digestion.
Comp. = complete digestion of fibrin; 0 = no digestion of fibrin (complete inhibition).

b. Alcohol modified pancreatic ferment solutions. A 10 per cent. solution of the same ferments was made in physiologic sodium chlorid solution, and after thorough shaking was filtered through hard-pressed paper. To the resulting filtrate was added 20 volumes of absolute alcohol and the mixture allowed to stand thirty minutes, resulting in the formation of a white precipitate. The mixture was then centrifugalized and the sediment rapidly resuspended in an amount of salt solution making the concentration 2 per cent. relative to the amount of pancreatic ferment powders originally employed.

EXPERIMENT 8.—*The Antitryptic Action of Immune Serum.*—I employed the serums of eleven immunized rabbits and eight normal rabbits for this experiment. For the determination of antitryptic action I used the method of fibrin digestion, as explained before, but I employed 0.35 c.c. of 1 per cent. native pancreatin solution filtered through a Berkefeld filter as antigen in this instance. I obtained the results shown in the chart; that is, the extent of the digestion of fibrin by pancreatin is markedly decreased in the immune serums as compared with the normal serums, although there is not so much difference in the partial digestions. These results indicate that the antitryptic power of serum is increased by immunization by pancreatin and trypsin, but there is no marked increase of this power in immunization by amylopsin.

EXPERIMENT 9.—*The Antitryptic Action of Immune Tissue Extracts.*—I used tissue extracts from twelve immunized rabbits and twelve normal rabbits (glycerin extracts as before) for determining inhibition against fibrin digestion by pancreatin, employing 0.2 c.c. of a 1 per cent. native pancreatin as a digestive agent in this instance.

The results obtained were as shown in Table 15. The tissue extracts of the eight normal rabbits had no inhibiting action against the digestion of fibrin with 0.2 c.c. of 1 per cent. pancreatin, while the tissue extracts of the immunized rabbits showed a marked inhibiting action against pancreatin, especially noticeable in the liver, kidney, spleen and bonemarrow; only a trace of inhibiting action was found with suprarenal capsule of the rabbits immunized with the pancreatin and none with the suprarenal capsule of rabbits immunized with amylopsin.

These results indicated that liver, kidney, spleen and bonemarrow of rabbits immunized with pancreatin and trypsin exhibited antitryptic power, signifying the production of antibodies against the antigen.

J. CHANGES IN QUANTITY OF GLUCOSE IN SERUM AND LIVER AFTER IMMUNIZATION WITH PANCREATIN

In 1916 Schäfer[58] asserted that when the pancreas is totally removed, grape sugar is no longer stored in the liver. This seemed to me a very interesting fact, because I also found a change in the quantity of grape sugar in serum and of glycogen in the liver in my experiments on immunization by pancreatin. I felt that if animals

57. Salkowski: Deutsch. med. Wchnschr., 1888, No. 16.
58. Schäfer: The Endocrine Organs, 1916, p. 2.

could be immunized with pancreatin there might be some change in the quantity of grape sugar in the serum, as well as of glycogen in the liver, so that I experimented with nine rabbits to ascertain the point.

EXPERIMENT 10.—*Quantitative Estimation of Glucose in Serum and Liver After Immunization by Pancreatin by Reduction with Fehling's Solution.*—For this experiment I used a 10 per cent. liver extract (with 50 per cent. glycerin) digested for twenty-four hours, and a half-normal serum tested within two hours after bleeding.

For a control I employed liver extract and half-normal serum of five normal rabbits. The results are shown in Table 16.

TABLE 16.—GRAPE SUGAR OF SERUM AND GLYCOGEN OF LIVER IN IMMUNIZED RABBITS

Number of Rabbit	Varieties of Immunization	Reduction of Fehling's Solution (1 C.c.)	
		10% Liver Extract (1 C.c.)	Half Serum (1 C.c.)
2	A. P.	+ (4)*	+
3	A. P.	+ (5)	±
4	A. P.	+ (5)	±
5	A. P.	0	±
6	A. P.	+ (4)	+ (2)
8	A. P.	+	+ (2)
9	N. P.	+ (4)	+ (2)
10	N. P.	+	+ (2)
11	N. P.	+ (5)	+ (3)
17	N. A.	+ (5)	+ (2)
18	A. A.	+ (5)	+ (3)
20	N. T.	+ (5)	+ (3)
5 normal rabbits, control		+ (6)	+ (4)

* The figure in parentheses following the + indicates the degree of reduction: + = slight positive; + (2) = ++, etc.; ± = trace; 0 = negative.

Table 16 shows that the quantity of grape sugar in the serum was markedly decreased in four cases and moderately decreased in five cases. The quantity of glycogen in the liver also was markedly decreased in three cases, moderately in three cases, and very slightly decreased in three cases after immunization with pancreatin. The decrease in the quantity of grape sugar in the serum and of glycogen in the liver is probably due to the fact that the antipancreatin affects the external secretion of the pancreas. In the immunization with amylopsin and trypsin a slight decrease is shown in the quantity of grape sugar in the serum and glycogen in the liver, as compared with the control cases, although only a few cases were tested.

SUMMARY AND CONCLUSIONS

1. Normal rabbit, guinea-pig, sheep and ox serum have an inhibiting action on pancreatic digestion.

2. The extent of the inhibiting action differs in different species of animals, but the quantity of the inhibiting substance is constant in each in relation to the others.

3. One c.c. of rabbit serum neutralizes 0.006 of pancreatin, and 0.1 c.c. of ox and sheep serum neutralizes 0.008 of pancreatin; also 0.1 c.c. of guinea-pig serum neutralizes 0.013 c.c. of pancreatin.

4. The inhibiting action of normal rabbit, guinea-pig, sheep and ox serums against pancreatic digestion is affected by heating; that is, fairly decreased at 56 C., and is lost by heating for thirty minutes at from 56 to 70 C., so that this inhibiting substance is fairly thermostabile.

5. Some normal serums show a precipitation with trypsin, but this phenomenon disappears on treating the serum with ammonium sulphate.

6. The inhibiting action of normal serum is decreased in a slight degree on treating the serum with ammonium sulphate.

7. I conclude from my various experiments that normal serum contains "pseudo-antiferment" (especially "pseudo-antitrypsin" in this instance).

8. The inhibiting activity of the serum also is decreased more or less by the production of anticomplement and antipseudo-antiferment (especially antipseudo-antitrypsin in this instance).

9. A tryptic enzyme appears in small amount in normal rabbit urine.

10. No antitrypsin was found in normal rabbit urine, and no antitryptic action against pancreatic digestion.

11. On the essential nature of the inhibiting power of normal serum against pancreatin, I propose that there exists nonspecific "pseudo-antitrypsin" as the product of physiologic function of tissue cells, so that this "pseudo-anttiferment" is of important significance for the antiferment action of serum, and also, as secondary factors, the albumin fraction and the complement of serum are associated with it.

12. Pancreatin introduced into the blood stream of rabbits is fixed by some of the fixed tissue cells, and seems to keep its activity during two days.

13. The possibility of tissue cells phagocyting pancreatin seems marked in the hemopoietic organs within one hour after injection, although pancreatin is also fixed by other organs.

14. The antigen (pancreatin) exists in the blood stream for two hours after injection.

15. The antigen (pancreatin) introduced into the blood stream is excreted into the urine in small amount.

16. The antitryptic power of the serum is increased by immunization by pancreatin and trypsin, and also by amylopsin, though in a slight degree.

17. The tissues of rabbits immunized with pancreatin and trypsin have a strong antitryptic power, especially the liver, kidneys, spleen, and bonemarrow; and also in a slight degree after amylopsin.

18. The quantity of grape sugar in the serum, and of glycogen in the liver, is decreased by immunization with pancreatin; and also in a slight degree after trypsin and amylopsin.

I wish to express my sincere thanks to Prof. P. Kyes for his interest and many helpful suggestions.

CHRONIC CAPILLARY CYANOSIS*

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Although general clinical conceptions of the mechanism of cyanosis are vague, it has long been recognized that it may be due to four main causes: (1) deficient oxygenation of the blood; (2) obstruction to normal flow in the capillaries; (3) combinations of 1 and 2, and (4) chemical transformation of the hemoglobin.

Demonstration of the mechanism of the form arising in the capillaries, has, so far as we have been able to determine, not been made and it is conceivable that it might prove important from the standpoint of diagnosis in obscure cases. The first question to decide in such a case would be whether the cyanosis could be due to insufficient oxygenation of the blood. In this connection it is well to emphasize, as Hoover[1] has recently done, that cyanosis arising in the thorax is always due to the passage of venous blood to the left heart. In pneumonia the blood cannot be oxygenated because of exudate in the alveoli, in edema of the lungs because of moisture in the form of foam in the alveoli, in congenital heart disease because of an abnormal opening between the venous and arterial sides of the heart, and in advanced emphysema because of a breaking down of the delicate structures which form the oxygenating surface.

Can we measure by any means the respiratory surface and so estimate the diminished oxygenating power of the lung as a whole? Peabody and Wentworth[2] have determined the vital air in normal individuals arranged in groups according to height. Thus, the average vital capacity of men 6 feet or over was 5,100 c.c., of men from 5 feet 8½ inches to 6 feet was 4,800 c.c., and of men from 5 feet 3 inches to 5 feet 8½ inches was 4,000 c.c. They did not determine the vital air in pneumonia but found that in individuals with large pleural effusions and consequent collapse of the lung the vital capacity varied between 74 and 42 per cent. of the normal. The vital air, then, may serve as a means to determine the functionating area of the lungs

* Submitted for publication Oct. 21, 1918.
* From the medical laboratories of the University of California Hospital.

1. Hoover, C. F.: Moisture in the Air Spaces of the Lungs and Oxygen Therapy, J. A. M. A., **71**:880, 1918.

2. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration. IV. The Vital Capacity of the Lungs and its Relation to Dyspnea, ARCHIVES INT. MED., **20**:443, 1917.

provided the respiratory center is in a condition of normal irritability and acidosis is not present. For a patient with acidosis will be able to hold his breath for a shorter period because of the tendency of a smaller amount of carbon dioxid to turn the hydrogen-ion concentration of his blood toward the acid side and stimulate his respiratory center.

If obstruction to the passage of blood through the capillaries is a cause of cyanosis, what will be the effect on the alkaline reserve in the tissues, on the number and oxygen content of the red cells, on the viscosity of the blood, and the total metabolism? Cannon, Frazer, and Hooper[3] have recently pointed out that concentration of blood in the capillaries, acidosis, and low blood pressure are invariable in shock; and it may be inferred that stagnation of the corpuscles is a factor in the development of the acidosis. Bence[4] has shown that higher carbon dioxid content of the blood increases its viscosity. Van Slyke[5] has recently published a method which permits of determination of both the oxygen capacity and the oxygen content of venous blood. It is obvious that it is the difference between these two which represents the amount of oxygen used in the capillaries, provided always that the blood is thoroughly oxygenated in the lungs. In a series of eleven normal individuals this oxygen unsaturation,[6] or oxygen consumption value, averaged 6.04 volumes per cent., the highest being 8.83, and the lowest 3. As the oxygen capacity is fixed by the hemoglobin of the corpuscles it is a reliable index of their hemoglobin content and may be used clinically as such. The hemoglobin as determined by this method varied from 116 to 94.5 per cent. and averaged 105.7 per cent. in the same series of normal subjects. Peabody, Meyer, and DuBois[7] have studied the total metabolism in cyanotic patients with cardiac decompensation and found it normal.

The recent presence in the medical ward of the University of California Hospital of two patients with chronic cyanosis has offered opportunity for a study of this phenomenon by modern methods.

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3. Cannon, W. B.; Fraser, J., and Hooper, A. N.: Some Alterations in Distribution and Character of Blood in Shock and Hemorrhage, J. A. M. A., **70**:526, 1918.

4. Bence, J.: Klinische Untersuchungen uber die Viskosität des Blutes, Ztschr. f. klin. Med., **58**:203, 1906.

5. Van Slyke, D. D.: Gasometric Determination of the Oxygen and Hemoglobin of Blood, J. Biol. Chem., **33**:127, 1916.

6. Lundsgaard, C.: Studies of Oxygen in the Venous Blood, J. Biol. Chem., **33**:133.

7. Peabody, F. W.; Meyer, A. L., and DuBois, E. F.: The Basal Metabolism of Patients with Cardiac and Renal Disease, ARCHIVES INT. MED., **17**:981, 1916.

REPORT OF CASES

CASE 1.—T., a Danish machinist, aged 37, entered the hospital Sept. 2, 1918, complaining of shortness of breath. Two years before admission, following an injury with a drill, he developed an infection of his hand which necessitated wide incision and drainage. After recovery he became progressively more short of breath and blue about his face. Examination showed a marked cyanosis of his lips, ears, and cheeks, fairly marked dyspnea on exertion, and dulness to the right and left of his upper sternum which the roentgen ray showed to be due to a persistent thymus. There was a barely audible tricuspid murmur, a moderately enlarged heart, and a slightly enlarged liver that projected 4 cm. below the costal margin. Such signs of decomposition as edema of the extremities and ascites were not present, but the urine contained a trace of albumin. The lungs and mediastinum were clear and the Wassermann reaction negative. While it was felt that the cyanosis was probably due to increased pressure in the great veins brought about by a weakened right heart, the lack of any usual etiology for heart disease, the apparently minimal leak at the tricuspid valve, the total absence of edema, and the presence of the persistent thymus were features which perhaps warranted the search for other possible factors in its causation.

CASE 2.—E., an American traveling salesman, aged 33, entered the hospital Sept. 10, 1918, complaining of shortness of breath and weakness. He had had Neisser infection five or six times. Six years before admission he lost 85 pounds during an attack of typhoid fever, and though he subsequently regained some weight, he lost it again so that his weight was only 135 pounds. He never recovered his strength after this illness and had shortness of breath, palpitation, and increasing cyanosis, especially for the last two years. There was some cough but only after excessive smoking. Examination showed marked grayish pigmentation and diffuse cyanosis, particularly of the face and mucous membranes, clubbed fingers, and a slightly enlarged spleen. There was marked venous pulsation in the neck, and movement of the lung bases behind was slightly restricted, but the chest otherwise expanded well and there were no râles. Roentgen-ray examination showed a small central heart and old root glands with diffuse grayness of both tops probably indicating an old healed tuberculosis. The blood pressure was 110-50, the Wassermann one plus, and the von Pirquet slightly positive. There were a few leukocytes in the urine. This patient had been studied before admission but because of the evidence of old disease of the lungs a diagnosis of polycythemia had been only tentatively made.

The table shows the laboratory data in both cases. Determination of the oxygen capacity, oxygen content and hemoglobin percentage was made by the Van Slyke method[5] and the colorimetric method of Palmer[8] was used as a check. The alveolar air was determined with the Fredericia[9] instrument and the vital air with an ordinary spirometer. Hematocrit readings were made by centrifuging oxalated blood at high speed in graduated 15 c.c. tubes under paraffin oil. Blood viscosity was roughly measured and expressed in multiples of the time required by a given amount of distilled water to drop from a pipet with

8. Palmer, W. W.: Colorimetric Determination of Hemoglobin, J. Biol. Chem., **33**:119.

9. Fredericia, L. S.: Eine klinische Methode zur Bestimmung der Kohlensaurenspannung in der Lungenleft, Berl. klin. Wchnschr., **51**:1268, 1914.

capillary opening. The plasma bicarbonate was determined by the method of Van Slyke.[10]

TABLE GIVING LABORATORY DATA OF CASES REPORTED

	Case 1 (T)	Case 2 (E)
Red Blood Corpuscles:		
Capillary	6,600,000	6,100,000
Venous	5,600,000	6,500,000
Hemoglobin:		
Capillary, per cent.	161	166
Venous, per cent.	156	166
Hematocrit (venous blood), per cent.	40.2	45
Viscosity (venous blood)	5.5	6
Plasma bicarbonate, volume per cent.	52.8	55.7
Alveolar air, mm. Hg	29.9	31.8
Oxygen capacity (venous blood), volume per cent.	29.05	29.5
Oxygen content (venous blood), volume per cent.	6.28	14.6
Oxygen unsaturation, volume per cent.	22.77	14.9
Vital air, per cent. of normal	75	73

DISCUSSION

It will be seen from a study of the data presented that both subjects had high peripheral red counts, hemoglobin percentages, oxygen unsaturation values, and viscosity, while the vital air, alveolar carbon dioxid and plasma bicarbonate were lowered in each case. Calculation of the color indexes gave figures far above the usual ones and in the presence of normal blood smears this feature cannot be satisfactorily explained. Such high oxygen unsaturation values in the absence of any cause for anoxemia of the blood coming from the pulmonary veins, suggests very strongly that much more oxygen was absorbed from the blood in its passage through the capillaries than normally, and since cyanosis itself is not accompanied by an increase in total metabolism, are proof that the blood was delayed in its passage from the arterial to the venous side.

The question now arises whether the otherwise unexplained acidosis found in both these subjects was due to this delay as Cannon supposes that it is in shock. Oxidation must be going on in the tissues at a normal rate but the carrying away of intermediary acid metabolites may be so delayed that the alkaline reserve is lowered, and it seems probable that in the absence of other sufficient causes the acidosis may be explained on this basis. Diminution in the vital air must be considered as due to the demonstrated slight acidosis and not to any decrease of the respiratory surface.

The normal venous count in T. shows that the blood was concentrated in the capillaries, and this constitutes the one essential difference

10. Van Slyke, D. D., and Cullen, G. E.: The Bicarbonate Concentration of the Blood Plasma, Its Significance and Its Determination as a Measure of Acidosis, J. Biol. Chem., **30**:289.

in the laboratory findings of the two cases. The significance of this concentration is not evident unless we assume that it was caused by dilation of the capillaries from back pressure.

It is obvious, then, that a solution of the clinical difficulties cannot be obtained from the laboratory data. There is scarcely any doubt as to the sufficient oxygenation of the blood in both cases, but we cannot say definitely that in E. there was not an increase in venous pressure, though the clinical evidence was against it. The high venous count here assumes possible importance as indicating a primary increase in the number of the red corpuscles and viscosity of the blood as a cause of the cyanosis. In the case of T. the slight tricuspid leak and enlarged heart make increased venous pressure most probable, but why this was not accompanied by edema is not clear.

In conclusion, the following tentative explanation of the mechanism of the form of cyanosis under discussion is given:

Cyanosis arises in the capillaries from increased oxygen unsaturation of the blood secondary to its delay in passage from the arterial to the venous side. This delay may be due to increased venous pressure or a primary increase in the red blood cells and viscosity of the blood. It lowers the alkaline reserve by increasing the concentration of acid metabolites in the tissues and thus diminishes the carbon dioxid carrying power of the blood, the alveolar carbon dioxid and the vital air.

A REPORT ON GOITER AMONG DRAFT MEN FROM THE NORTHWEST *

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During the May and June examinations of western drafted men at this depot, a remarkable number of thyroid enlargements were noted. Many were unassociated with toxic symptoms, and at first no exact record was made beyond a simple notation of the condition. It soon became evident, however, that a considerable proportion of the cases had true hyperthyroidism and were unfit for general military service. These men were studied with especial reference to nervous and vasomotor instability and cardiac and renal function, and the results tabulated.

Below are noted the quotas from the several states with number of goiter rejections opposite:

State	Quota	Rejected for Goiter
Oregon	2,850	23
Montana	354	5
California	4,550	4
Nevada	49	3
Utah	168	1
Idaho	165	1
New Mexico	405	0
Arizona	318	0
Wyoming	92	0
Total number examined	8,951	
Total number rejected		37

Evidently there are "goiter areas" in certain of the Northwestern States, notably Oregon and Montana. The high percentage in the Nevada contingent scarcely can be considered because of the small number of men examined.

The detailed findings in thirty-four cases are recorded in Table 1. Of this number, six had very large goiters; twelve had moderate and thirteen slight enlargements. All the Montana cases had marked enlargement; three were very large and would interfere with wearing of uniform and pack. One was causing pressure symptoms, manifested by chronic hoarseness and periods of suffocation. One had been operated on in July, 1917, and had recurred. Twenty had notable

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TABLE 1.—DATA OF FIRST CONTINGENT*

Case Number	Family History	Locality from Which Sent		Description of Thyroid	Tremor of Hands	Eye Findings				Heart Findings				Blood Pressure		Urinalysis		
		City	State			Stellwag's Sign	Von Graefe's Sign	Moebius' Sign	Exophthalmos	Tachycardia	At Rest	Immediately after 100	Two Min. After	Systolic	Diastolic	Albumin	Hyalin Casts	Granular Casts
1	—	Ketchikan.....	Alaska	Mod.	—	—	—	—	—	Mod.	96	120	100	160	115	Trace	—	—
2	—	Hanford.....	Calif.	Mod.	Mod.	+	+	—	—	Mod.	†							
3	—	Oakland.....	Calif.	Mod.	Mod.	+	+	—	—	Marked	†							
4	—	San Francisco..	Calif.	Mod.	Mod.	—	—	—	—	Marked	128	170	140	165	100	Trace	+	+
5	Mother and sister	Yreka.....	Calif.	Slight	Mod.	—	—	—	+	Mod.	88	120	90	†				
6	—	Oakland.....	Calif.	Mod.	Slight	—	—	—	—	Mod.	96	138	112	155	90	Trace	+	+
7	—	Unknown.....	.....	Mod.	—	—	—	—	—	Mod.	108	128	114	150	100	Trace	+	+
8	—	San Jose.....	Calif.	Slight	Slight	—	+	—	—	Marked	†							
9	—	Blackfoot.....	Idaho	Slight	—	—	+	+	+	†								
10	—	Niefy.....	Utah	Slight	Slight	+	+	+	+	†								
11	—	Carson City....	Nev.	Marked	—	—	—	—	—	—	84	102	78	140	70	Trace	+	+
12	—	Reno.....	Nev.	Marked	Slight	+	+	+	+	Mod.	108	126	114	150	95	Trace	+	+
13	—	Reno.....	Nev.	Mod.	—	—	—	—	—	—	70	78	72	162	100	+	+	+
14	—	Hamilton.....	Mont.	Mod.	Slight	+	+	+	—	Slight	†							
15‡	—	Forsyth.....	Mont.	Marked	—	—	—	—	—									
16‡	—	Forsyth.....	Mont.	Marked														

* This table consists of cases rejected on the first contingent received. We had but one blood pressure instrument, a Tycos, which was continually breaking or out of order. Our records were not as complete in detail as the later series. The later series are accurate results. The blood pressure having been taken by Mercer instrument, mercury type, thus eliminating errors due to spring and all results were carefully recorded.

17¶	—	Livingston.....	Mont.	Marked	—	—	—	—	—	—	76	120	84					
18	—	Baker.....	Ore.	Mod.	—	—	—	—	—	Mod.	120	160	120	—	—	Heavy	Marked	
19	—	Coquilla.....	Ore.	Slight	Slight	—	—	—	—	Slight	90	140	96	116	80	†		
20	—	Eugene.....	Ore.	Mod.	Slight	—	+	—	+	—	†							
21	—	Eugene.....	Ore.	Mod.	—	—	—	—	—	Mod.	104	144	120	—	—	Heavy	Heavy	Heavy
22	—	La Grande.....	Ore.	Slight	Marked	+	+	—	—	Mod.	96	135	102	†				
23	—	Minneville.....	Ore.	Mod.	—	—	—	—	—	Mod.	118	140	120	150	90	+	Heavy	Heavy
24	—	Pendleton.....	Ore.	Mod.	Slight	—	—	—	—	Marked	102	180	130	†				
25	Brother and sister	Pendleton.....	Ore.	Marked	Mod.	—	—	—	—	Mod.	120	144	120	160	90	Heavy	+	+
26	—	Portland.....	Ore.	Slight	—	—	—	—	—	Mod.	104	128	120	150	95	+		
27	—	Portland.....	Ore.	Slight	—	—	—	—	—	Mod.	94	144	108	160	90	+	+	+
28	—	Portland.....	Ore.	Mod.	Slight	—	+	—	—	Mod.	104	120	100	140	70	—	—	—
29	—	Portland.....	Ore.	Mod.	—	—	—	—	—	Marked	120	150	124	—	—	+	—	—
30	—	Portland.....	Ore.	Slight	Slight	—	—	—	—	Mod.	90	144	100	145	90	Trace	—	—
31#	—	Portland.....	Ore.	Slight	—	—	—	—	—	Marked	128	136	114					
32	—	Portland.....	Ore.	Slight	Slight	—	—	—	—	Marked	120	136	120	125	80	—	—	—
33	—	Portland.....	Ore.	Slight	Slight	—	—	—	—	Marked	120	158	120	135	80	—	—	—
34	—	Tacoma.....	Wash.	Slight	—	—	—	—	—	Mod.	96	135	108	—	—	—	—	—

† Not recorded.
‡ Size interfering with uniform wearing.
§ Causes pressure symptoms and interferes with uniform wearing.
¶ Interferes with uniform.
# Rejected for other causes.

fine tremor; ten had ocular symptoms, and all but five had tachycardia —that is, pulse of 90 or above at rest. There were eight with a standing pulse rate of over 100, and twelve with a rate of 115 or over. Leaving out of consideration the five cases without tachycardia, eight had a pulse count of from 120 to 140 after the standard hopping test (fifty hops on each foot); eight had a count of from 140 to 180, and all were dyspneic. In but three did the rate, two minutes after exercise, return to the original rate. Of eighteen blood pressure estimations, eleven were 150 or above and only three were below 140. Nearly all men showed a trace of albumin in the urine, and several had a definite nephritis.

In July, two contingents of 1,350 men each were received, chiefly from Oregon and California. Of the first 1,250 men from Oregon, 151 had sufficient thyroid enlargement to justify notation to that effect. Sixty cases were tabulated (Table 2).

The question of family history was discussed carefully with forty-eight men, twenty-one of whom gave a positive history and twenty-seven a negative. In fifteen instances female relatives were affected, in three, male, and in three both male and female.

The personal history was variable. Most of the men were farmers or woodsmen, and the great majority were of good physique. Some were not aware of any abnormality whatever; others had noticed a slight fulness of the neck or recalled, when questioned, that they wore a larger collar than formerly, but had no subjective symptoms. Others complained of "nervousness," palpitation and periods of suffocation. Some admitted excitability, quick temper, and fatigue on moderate exertion. Excessive perspiring and diarrhea were mentioned in a few instances. Loss of weight was common and, in several cases, marked. In practically every instance the foregoing symptoms, with the exception of palpitation, were elicited only after persistent cross examination. Almost never did the patient consider that his goiter had any bearing on his condition. The palpitation he attributed to too many cigarets or late hours.

Six of the goiters were large, twenty-two moderate, and thirty-two small.

Tremor of the hands was almost always present, though at times slight, and somewhat coarse. Like the palpitation it was attributed to cigarets in many cases.

Marked eye signs were uncommon. Only five men showed distinct exophthalmos, although almost all had a slight widening of the palpebral fissures. Poor convergence was relatively frequent.

Tachycardia was the rule; thirty-six cases having a standing rate of over 90, and twenty-eight of over 100. In over half the cases the

response to exercise was poor. Hypertension was present in a variable degree; thirty-three cases had a systolic pressure of over 140. In four cases a second reading, taken one or two days after the first, was notably lower than the original reading. This accords with a vasomotor instability that reasonably may be considered toxic although no organic arterial change has occurred.

Albuminuria was noted in but two cases, and considered as a whole, there were fewer severely toxic cases than in the earlier group. Possibly this was due to more strict elimination by local draft boards. The relative toxicity among the two groups, as indicated by the percentage showing the various specific symptoms is given below:

	May and June Group, Per Cent.	July Group, Per Cent.
Tremor	66	61
Tachycardia:		
Pulse 90 to 100	83	18⅓
Pulse over 100	66	46
Poor recovery after exercise	90	33
Blood Pressure over 140	83	55
Albuminuria	83	3⅓

The subsequent history of the men with palpable thyroids or nontoxic goiters who were enlisted is an interesting speculation. It may be that the change in location and mode of life will cause the gland to resume normal proportions. On the other hand, it seems more likely that the stress and nervous tension incident to army life will greatly aggravate the potential nervous and vasomotor instability and eventuate in a speedy break-down.

CONCLUSIONS

1. Goiter is more common in young men than the experience of the general practitioner would suggest.

2. There are definite goiter districts in Oregon and Montana and probably in Nevada.

3. Locality appears to be much greater in importance than family tendency.

4. Many of the goiters in draft men are unmistakably toxic and should be cause for rejection.

5. The more toxic cases show a tendency to nephritis, in addition to the classical cardiac symptoms.

6. All men having thyroid enlargement should be examined systematically for evidence of cardiorenal pathology.

TABLE 2.—Data of Later Contingents

Case Number	Family History	Locality from Which Sent		Description of Thyroid	Tremor of Hands	Eye Findings				Heart Findings				Blood Pressure		Urinalysis			Disposition*
		City	State			Stellwag's Sign	Von Graefe's Sign	Moebius' Sign	Exophthalmos	Tachycardia	At Rest	Immediately after 100	Two Min. After	Systolic	Diastolic	Albumin	Hyalin Casts	Granular Casts	
1	—	San Francisco.	Calif.	Slight	—	—	—	—	—	—	68	102	70	130	85	—	—	—	E
2	—	Seattle.....	Wash.	Slight	—	—	—	—	—	—	96	120	88	133	85	—	—	—	E
3	—	Tucson.....	Ariz.	Slight	Slight	—	—	—	—	—	76	118	90	135	83	—	—	—	R
4	—	Reno.....	Nev.	Mod.	—	—	—	—	—	—	72	102	74	130	85	—	—	—	E
5	—	Aurora.....	Nev.	Slight	Slight	—	—	—	—	—	60	100	60	135	83	—	—	—	E
6	—	Jacksonville....	Ore.	Slight	Slight	—	—	—	—	—	84	115	104	140	90	—	—	—	E
7	—	San Jose.....	Calif.	Slight	—	—	—	—	—	—	80	108	80	140	90	—	—	—	R
8	—	San Jose.....	Calif.	Palpable	—	—	—	+	—	Mod.	88	102	96	145	100	—	—	—	E
9	—	Reno.....	Nev.	Palpable	—	—	—	—	—	—	74	90	78	130	80	—	—	—	E
10	—	San Francisco..	Calif.	Mod.	—	—	—	—	—	Slight	96	124	92	135	85	—	—	—	E
11	—	Vancouver.....	Wash.	Slight	Slight	—	—	—	—	—	78	108	84	115	75	—	—	—	E
12	—	Washington....	D. C.	Slight	—	—	—	+	—	—	72	102	90	130	80	—	—	—	R
13	—	San Francisco..	Calif.	Mod.	—	—	—	—	—	—	80	102	80	135	90	—	—	—	E
14	—	Woodburn.....	Ore.	Slight	—	—	—	—	—	Mod.	120	156	114	130	85	—	—	—	R
15	Sister	McMinnville....	Ore.	Mod.	Slight	—	—	—	—	Mod.	114	138	120	130	80	—	—	—	E
16	—	Dallas.....	Ore.	Slight	—	—	—	—	—	Mod.	102	150	108	120	87	—	—	—	E
17	—	Hillsboro.....	Ore.	Mod.	Slight	—	—	—	—	Mod.	114	154	108	140	90	—	—	—	E
18	—	Eugene.....	Ore.	Mod.	Slight	+	—	Sl.	—	Slight	96	138	110	150	85	—	—	—	E
19	—	Dallas.....	Ore.	Slight	—	—	—	—	—	Marked	145	176	144	140	102	—	—	—	R
20	Mother and sister	Grants Pass....	Ore.	Large	Slight	—	+	+	—	Marked	135	170	132	170	110	—	—	—	R
21	Two sisters	Jacksonville....	Ore.	Slight	—	—	—	Sl.	—	Slight	96	116	96	160	120	—	—	—	E
22	Grandmother	Jacksonville...	Ore.	Slight	Slight	—	—	Sl.	—	Mod.	108	144	108	150	100	—	—	—	R

23	—	Coquille.....	Ore.	Slight	+	—	—	+	—	Mod.	114	154	120	150	110	—	—	—	R
24	—	Jacksonville....	Ore.	Slight	Slight	—	—	+	—	Slight	96	126	96	160	120	—	—	—	R
25	—	Woodburn.....	Ore.	Slight	+	—	—	—	—	Mod.	120	156	150	148	95	—	—	—	R
26	—	Salem.....	Ore.	Mod.	Slight?	—	+?	—	—	Mod.	108	138	114	130	80	—	—	—	E
27	—	Salem.....	Ore.	Slight	—	—	—	—	—	Marked	120	152	114	138	80	—	—	—	E
28	Father and aunts	Corvallis.....	Ore.	Mod.	+	—	+	—	—	Marked	120	132	120	160	120	—	+	+	R
29	—	Eugene.....	Ore.	Palpable	Slight	—	—	—	—	Mod.	102	140	120	150	85	—	—	—	E
30	—	Hillsboro.....	Ore.	Diffused	Marked	—	—	—	—	Slight	90	114	102	150	88	—	—	—	R
31	—	Hillsboro.....	Ore.	Marked	Marked	—	—	+	—	Slight	90	130	96	142	72	—	—	—	R
32	Sister and 4 children	Dallas.....	Ore.	Mod.	Slight	—	—	—	—	—	72	100	72	128	76	—	—	—	E
33	Mother	Portland.....	Ore.	Mod.	Mod.	+	+	—	—	Slight	96	100	96	154	80	—	—	—	R
34	—	Portland.....	Ore.	Mod.	Fine	—	—	—	—	—	84	132	114	138	88	—	—	—	R
35	Sister	Portland.....	Ore.	Mod.	Fine	—	—	—	—	—	84	132	114	138	88	—	—	—	R
36	—	Portland.....	Ore.	Slight	—	—	—	—	—	Mod.	108	140	115	114	62	—	—	—	R
37	—	Portland.....	Ore.	Slight	Fine	—	—	—	+	Mod.	108	150	124	168	70	—	—	—	R
38	Mother and sister	Portland.....	Ore.	Slight	—	—	—	—	—	Mod.	102	144	108	108	56	—	—	—	R
39	Mother	Pendleton.....	Ore.	Mod.	—	+	—	—	—	Mod.	116	160	120	142	74	—	—	—	R
40	—	Pendleton.....	Ore.	Slight	Coarse	—	—	—	—	—	84	114	88	150	86	—	—	—	E
41	—	Prineville.....	Ore.	Slight	Fine	—	—	—	—	Slight	96	112	104	158	68	—	—	—	R
42	Five sisters, mother; 1 sister died	Portland.....	Ore.	Simple	—	—	—	+	—	—	72	90	70	112	72	—	—	—	E
43	Sister	Portland.....	Ore.	Mod.	Mod.	—	+	—	—	Marked	136	156	120	144	76	—	—	—	R
44	Sister	La Grande.....	Ore.	Slight	Fine	—	—	+	—	—	84	117	84	110	66	—	—	—	R
45	Mother	Portland.....	Ore.	Mod.	Mod.	—	—	—	+	—	72	96	90	144	84	—	—	—	R
46	Brother	Pendleton.....	Ore.	Slight	—	+	—	—	—	—	78	102	78	130	70	—	—	—	E
47	Brother	Portland.....	Ore.	Slight	—	—	+	—	—	—	88	128	114	124	74	—	—	—	R

TABLE 2.—DATA OF LATER CONTINGENTS—(*Continued*)

Case Number	Family History	Locality from Which Sent		Description of Thyroid	Tremor of Hands	Eye Findings				Heart Findings				Blood Pressure		Urinalysis			Disposition*
		City	State			Stellwag's Sign	Von Graefe's Sign	Moebius' Sign	Exophthalmos	Tachycardia	At Rest	Immediately after 100	Two Min. After	Systolic	Diastolic	Albumin	Hyalin Casts	Granular Casts	
48	Sister and brother	Portland.....	Ore.	Mod.	—	+	—	—	—	Mod.	105	141	111	140	87	—	—	—	R
49	Sister	Portland.....	Ore.	Marked	Slight	+	—	—	—	Slight	96	135	102	148	75	—	—	—	R
50	—	Portland.....	Ore.	Palpable	Fine	—	—	+	—	Mod.	108	144	112	150	88	—	—	—	R
51	Father, brother and sister	Portland.....	Ore.	Slight	Slight	—	—	—	—	Mod.	104	132	116	94	56	—	—	—	R
52	—	Portland.....	Ore.	Palpable	—	+	—	—	—	Mod.	108	120	108	150	94	—	+	+	R
53	Paternal aunt	Portland.....	Ore.	Mod.	—	+	+	+	—	—	84	120	93	140	86	—	—	—	R
54	—	Portland.....	Ore.	Mod.	—	—	—	—	—	—	60	75	48	125	85	—	—	—	E
55	—	Portland.....	Ore.	Slight	—	+	+	+	—	Mod.	108	135	99	112	75	—	—	—	R
56	—	Portland.....	Ore.	Mod.	Mod.	+	+	—	—	Slight	98	114	96	134	80	—	+	+	R
57	—	Portland.....	Ore.	Mod.	Mod.	+	—	—	+	Slight	90	141	117	168	93	+	—	—	R
58	Brother	Portland.....	Ore.	Mod.	Mod.	—	—	—	—	—	81	126	93	158	85	—	+	+	R
59	—	Portland.....	Ore.	Mod.	Slight	—	—	+	—	Mod.	108	130	112	138	78	—	—	—	E
60	Mother	Hanford.....	Calif.	Mod.	Marked	—	—	—	+	Mod.	102	132	114	130	80	+	+	+	R
61	—	Alhambra.....	Calif.	Slight	Slight	—	+	—	—	Mod.	104	138	104	125	80	—	—	—	E
62	—	Pasadena.....	Calif.	Mod.	Slight	+	—	—	+	—	88	114	86	140	82	—	—	—	E
63	—	Los Angeles....	Calif.	Slight	Slight	+	—	—	—	Mod.	104	140	104	128	76	—	—	—	E
64	—	McMinnville....	Ore.	Mod.	Mod.	+?	—	+	—	—	84	120	90	140	90	—	Few	Few	E

* R = rejected for military service.
E = enlisted for military service.

NONSPECIFIC THERAPY IN ARTHRITIS AND INFECTIONS

A STUDY OF THE CHANGES IN THE BLOOD CONSEQUENT ON THE INTRAVENOUS INJECTION OF TYPHOID PROTEIN

A CONSIDERATION OF THE ANALOGY BETWEEN THE TYPHOID PAROXYSM AND THE MALARIAL PAROXYSM *

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Many of the clinical effects of the intravenous injection of foreign protein have been known for some time, particularly since the introduction of intravenous dosage of diphtheria antitoxin in diphtheria.[1] It has been observed that, following a previous almost afebrile or slightly febrile period in the course of disease, a more or less pyrogenic reaction followed the intravenous injection of antitoxin. For example, of twenty-six recent cases from my records in the contagious hospital, treated by intravenous injection of antitoxin, twenty-one reacted with chill and rise of temperature. In some cases the rise in temperature was as high as 108 F.

The explanation of this reaction was not generally known until the researches of Vaughan and his co-workers were made (1909). Prior to this time, Buchner (1890), Krehl and Matthes (1895) had induced fever in animals by the subcutaneous injection of bacterial and other proteins.

No importance was attached to the protein reaction as a therapeutic measure until quite recently. Indeed, as yet no cognizance has been given to the possible effect of the foreign protein on the disease process

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* From the Department of Pediatrics and Contagious Diseases, University of Michigan Hospital, and the Cowie Hospital. Address before the Chicago Pediatric Society, May 21, 1918.

1. An Italian physician, Zamboni (Gazz. d. osp., 1900, **8**, 4), was the first to use antitoxin by the intravenous route. He reported increase of temperature following the injection. Von Behring (1901) (quoted from Beyer, München. med. Wchnschr., Aug. 26, 1913) recommended the intravenous injection in severe cases of diphtheria. Fette (Med. Klin., 1909, No. 50) reported 145 cases treated by intravenous injections of antitoxin, and he also records temperature reactions. Park (Boston M. and S. J., **168**:73, 1913) reported 200 cases, the first in America, treated by this method. He records chill, nausea, vomiting, fever, sweating and pain as common symptoms following the injection.

itself in diphtheria. Efforts have always been directed at minimizing the effect of the protein contained in the antitoxin.

The recent work on the remarkable effects of intravenous injections of foreign protein in arthritis by Miller and Lusk[2] and others has stimulated not only the usual therapeutic enthusiasm consequent on such reports, but also an interest in studies which may, in the first place, reveal what happens in the body after the foreign protein enters the blood stream; secondly, why these changes bring about an amelioration of symptoms and arrest disease processes; and thirdly, what its effect on the body tissues either for weal or woe may be.

Thus far it has been determined repeatedly that a typical protein reaction is characterized by chilliness or a definite chill, fever, pain, sweating, and characteristic changes in the formed elements of the blood, a leukopenia, followed by a leukocytosis sometimes of very marked degree.[3]

In 1912 Brown and Ross[4] reported that there was always a leukocytosis four to ten hours after an intramuscular injection of sodium nucleinate. The count went as high as 23,000 and returned to normal in from three to five days. This calls to memory the early work done in the University of Michigan on leukocytosis induced by the subcutaneous injection of nuclein (Vaughan, 1892). The explanation for this reaction is now elucidated.

We became interested in the changes in the formed elements of the blood. Unable to find any work on the successive cell changes, we directed our attention to this somewhat arduous task, with prospective reward, however, because either positive or negative results seemed to us to be of value. Through the courtesy of Dr. Newburg of the Department of Internal Medicine all adult cases of "arthritis" which did not clear up after the removal of all known foci of infection were referred to us for treatment. These together with three private cases make up our small list of ten carefully studied cases.

The first intravenous injections of typhoid protein (vaccine) we find are those reported by Ichikawa[5] in Japan. He records eighty-seven cases of typhoid fever treated in this way. An immediate rise in temperature and the end of the disease by crisis occurred in many of the cases.

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2. Miller and Lusk: J. A. M. A., **68**:764 and 1940, 1917. Boston M. & S. J., January, 1913.

3. Ewing's observations, 1895, are of interest in this connection (New York M. J., **62**:196, 1895).

4. Brown & Ross: J. Ment. Sc., **58**: 1912.

5. Ichikawa: Ztschr. f. Immunitätsf., **23**:32. 1914; abstr. in J. A. M. A., **64**: 546. 1915.

ORDER OF OUR INVESTIGATION

Controls.—In each case a control count preceded the injection or was made at the time of the injection. In a few a prolonged hourly or two hourly control count was made the day preceding the injection. For lack of time and assistance this could not be done in all cases. In Case 10 all the counts were made on 500 cells. In Case 8 most of the counts were on 500 cells. In all others 200 cells were counted. A 1/12 Leitz oil immersion lens was used in all counts. The leukocyte counts were always made in each case by the same person and were carefully checked. All differential counts were made by us and all abnormal and atypical cells were checked by both of us.

Total leukocyte counts and complete differentials were made starting from the beginning of injection, ½, 1, 1½, 2, 3, 4 and every hour thereafter until the height of the reaction or its end was reached in most cases. Great care was taken to observe closely in controls as well as subsequent counts the presence and the number of abnormal or atypical cells both in the white and the red groups.

A few observations were made on the platelets and also a few spectroscopic observations.

Parke, Davis and Company's typhoid vaccine was used. Two minutes were consumed each time in making the injection, which was always given at least six hours after a meal.

The roentgenographic records are from Professor Van Zwaluwenburg's reports excepting Case 1.

The ten cases were made up as follows:

2 chronic multiple periarthritis deformans
1 hypertrophic arthritis deformans
1 chronic multiple periarthritis deformans in a child with developmental epiphyseal changes
2 "acute rheumatism," polymuscular and periarticular
1 atrophic arthritis
1 hypertrophic spinal arthritis
1 gonorrheal vulvovaginitis
1 suppurative mastoiditis with chronic pulmonary tuberculosis

Four of these were children and six were adults.

REPORT OF CASES

CASE 1.—*Polyperiarthritis deformans, chronic.*

History.—Florence S., aged 11½, entered the Cowie Hospital Sept. 16, 1917, complaining of stiffness and contractures of the legs and upper extremities, cramps in the hips, fever and inability to walk.

Feb. 16, 1911, the patient had measles. The eruption did not "come out good." She had night sweats, was nauseated and had projectile vomiting until May. She was able to be up in July, when it was noticed that she dragged her right foot and leg. She had a severe cough following the measles. In August her head was drawn to one side for a period of three weeks and the arms were drawn up. In September it became impossible for her to walk and contractures began to develop. In October she had an attack of fever (recurrent attacks); her temperature went as high as 103 F., but she had no chills. In January, 1912, she came to the Pediatric Clinic. She was treated by Biers' hyperemic stasis. She began to walk in May, 1912, but it was fall before she walked well. In April, 1915, she had another attack of fever with "inflammatory rheumatism, neuritis and malnutrition" which lasted until September. At this time she walked stiffly, but was able to go seven blocks. The improvement continued until July, 1916, when she had another attack of measles. In November, 1916, she had a chill, temperature 105 F.; was nauseated and had projectile vomiting. Dec. 18, 1916, she had chills and fever, and since then

she had been unable to walk. During this month she had her tonsils and adenoids removed and was treated with an autogenous vaccine made from cultures from the tonsils, without improvement. During December and January she was given passive movements and hot baths. In December, 1917, she walked a few steps across the room. In May she was given stock vaccine without results.

She has always been constipated. In 1914 she had a skin eruption starting as tiny vesicles between the fingers. She now had scaling on the hands, and vesicles about the anus and on the inside of the thigh. The heart was negative.

Blood: Red cells, 4,600,000; whites, 7,200; polynuclears, 54 per cent.; small lymphocytes, 31 per cent.; large lymphocytes, 13 per cent.; transitionals, 2 per cent.

Urine, negative.

Roentgenographic (from Dr. A. W. Crane) report: "Sinuses all negative. Teeth negative. Abnormally dense areas about the hilum of each lung of tuberculous type, but may result from other kinds of infection. Spleen and liver slightly enlarged. Barium gastro-intestinal study negative. Hand, wrist and knee show a decalcifying process in the joint region; joint surfaces, however, are left emphasized, giving the appearance of egg shell fragility, especially the knee joint. The articulating surfaces are smooth. No erosions."

Nonspecific Protein Therapy Record.—This patient was given three injections (Fig. 1) of typhoid vaccine, to each of which she responded with chill, nausea, vomiting, temperature and leukocytic changes associated with pain localized in the back, arms, and legs. Following the second injection the fingers of the left hand became more flexible and it was now possible to insert two fingers between her fingers and palm; this had been impossible before. Following the third injection the patient felt like walking, and with assistance walked down the hall. This was the first time she had walked at all since the previous March (eight months). This day her knees were definitely more flexible than on her entrance and she could flex the toes.

CASE 2.—*Chronic periarthritis; no structural joint change.*

History.—Mrs. W., aged 59, entered the medical clinic, University Hospital, complaining of pain in the knees, inability to stand or walk, inability to freely move right elbow. Referred to us for treatment March 19, 1918.

Present illness began one year before admission with migrating swelling of the fingers, elbows and shoulders. Three months later the knees became involved, swollen and tender. The fingers and shoulders were better, the right elbow and knees were still involved, the third left finger had one thickened joint. She was unable to stand or walk. The patient had a course of serum treatment, but no chills, fever or pain resulted.

Aside from marked wasting of the musculature of the extremities, contracture of right elbow and knees, marked swelling of the knees (periarticular —no floating of patella), examination was negative. The heart had soft blowing systolic murmur at apex, without enlargement or displacement.

Infected teeth and tonsils had been removed.

Roentgen Report.—The skull showed extensive atrophic changes and therefore was more than ordinarily difficult to read. The frontals were voluminous and air-containing; the ethmoids were very narrow and difficult to see, probably denser than normal, but judgment was difficult because of the bilateral involvement. The antra were small, thin walled and apparently normal. The nasal passages were unusually wide; probably an atrophic rhinitis. The sphenoid was very small, and was scarcely to be distinguished in the density of this region. Diagnosis: Bilateral posterior ethmoiditis. No roentgenogram of joints made.

The patient made no improvement and was referred to us for nonspecific protein treatment.

Nonspecific Protein Therapy Record.—This patient received ten intravenous injections of typhoid vaccine, dosage 1 billion (Fig. 2). Following the first,

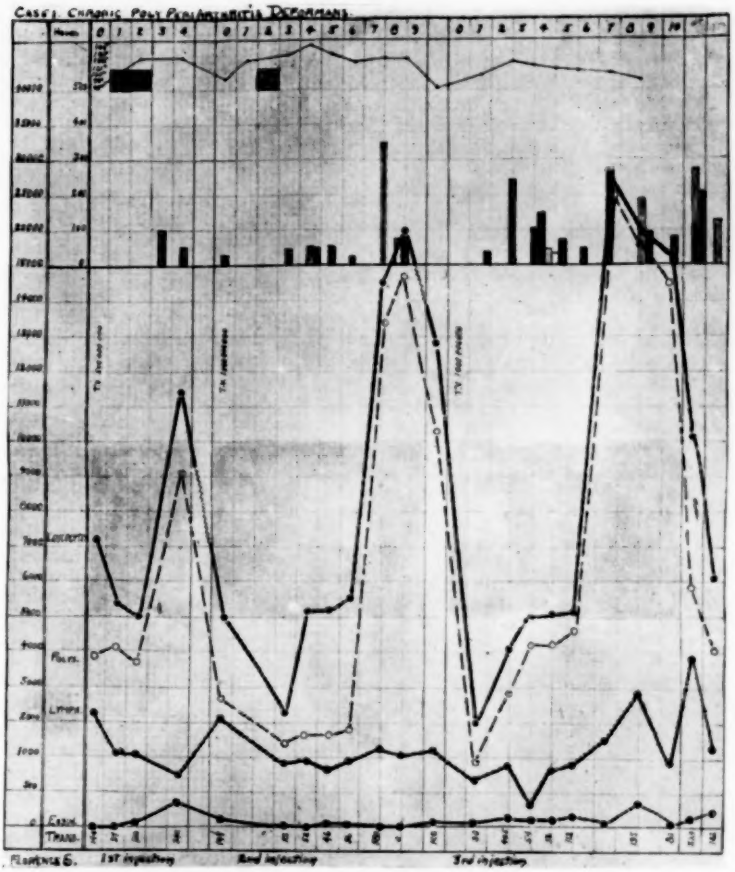

Fig. 1.—Case 1. Chronic polyarthritis deformans. In this and the following charts black columns = myelocytes; white colums = basophil polynuclears; gray columns = atypical cells; squares at top = nucleated reds. The absolute count for blood cells is given in the column at the left. The abnormal cells are drawn on a base line in the upper half of the chart, the absolute count being given in the second column of figures to the left. The black columns represent myelocytes, the white basophilic polynuclears, and the gray the number of atypical cells. The shaded blocks between five thousand and ten thousand represent the normal limits for the total leukocyte count during each reaction. Nucleated red blood corpuscles are indicated by squares at the top of the chart, the figure indicating the number seen during the differential count. The transitionals per cubic millimeter are given in figures at the bottom of the chart. The temperature curve is indicated at the top of the chart.

which caused a slight clinical reaction, her right arm was more stiff than before. After the sixth injection the patient said that for the first time she was able to straighten out her legs and she thought the treatments were benefiting her, but she complained of swelling of the ankles. The chill in the first six reactions was present, but was slight. Following the seventh reaction her knees were swollen, but she could bend and move them without pain and she was very

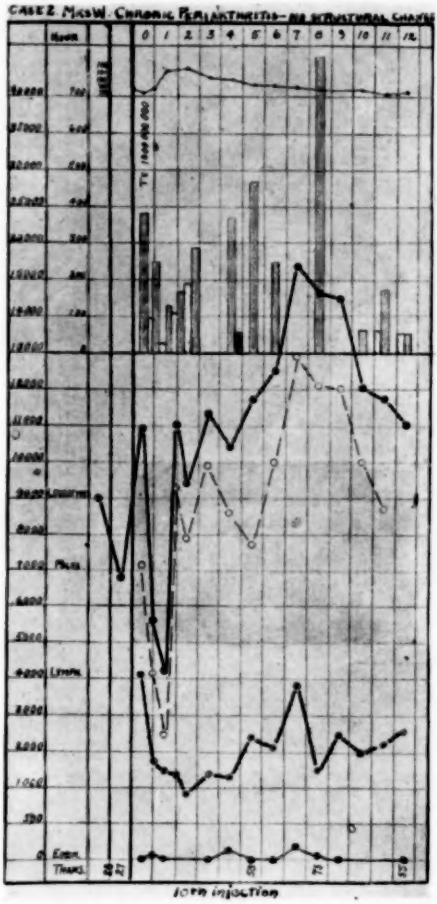

Fig. 2.—Case 2, Mrs. W. Chronic periarthritis. No structural change.

anxious to attempt to walk. Following the eighth injection she was allowed to walk and took about ten steps. The tenth reaction is recorded on the chart (Fig. 2). She was at the time of the report able to get about by hanging on to the bed and chairs. She stood straighter than previously and showed considerable improvement. The injections were made on the following dates: March 20, 24, 27, and 31; April 3, 6, 11, 13, 16 and 20. Each injection showed the characteristic reaction.

CASE 3.—*Polyperiarthritis deformans, chronic, infectious.*

History.—Blais, farmer, aged 59, entered the medical clinic Jan. 10, 1918, complaining of pain and swelling and stiffness of many joints, and muscle pain.

The family history was negative.

The present illness began about sixteen years prior to admission with pains in the back, chiefly during the winter months. Three or four days' rest in bed served to clear up the attacks. These attacks occurred frequently until six years prior to admission when they became more severe, and his "hands swelled." He was given intramuscular injections every day for four or five weeks with no benefit. He then took a series of hot baths in conjunction with subcutaneous injections for three weeks; no improvement. After this he took a course of subcutaneous injections of "rheumatic serum" which gave him much relief. At the end of the first week he was markedly improved and was able to return to work. He continued to work until last November, but at no time did the symptoms completely disappear. He was well enough so that he could work; much of the time there was considerable pain in his joints and muscles. This had recently become worse.

Physical Examination.—Large frame; well nourished; large musculature; no teeth; tonsils infected; patient almost entirely helpless; has to be helped from chair to bed; could not remove his shirt or raise his arms above his shoulders; limitation of neck movement. Joints showed marked deformity of metacarpal-phalangeal joint; fingers held in part flexion and stiff; complete extension could be obtained with only a little pain; marked deformity of fingers of both hands and of the left thumb; elbows cannot be completely extended; rotation of shoulder joints markedly limited; knees held in partial flexion; cannot be extended. Some ankylosis of the hips; the pelvis tilts when the leg is raised; the involvement of the joints, for the most part, is periarticular. The roentgenogram showed that the bones themselves are but slightly involved.

The lungs, heart and abdomen are negative.

The tonsils were removed, as they contained large and small pus pockets. The patient was given a course of large doses of acetyl salicylic acid without noteworthy result.

Wassermann negative. Urine negative.

Blood count: Reds, 5,100,000; whites, 8,200; hemoglobin, 70 per cent.

Roentgen Report.—(Dr. Van Zwaluwenburg.) Dorsopalmar stereogram of hands shows extensive deformity, with comparatively little destruction of the bones. Certain of the articulations show an inconsiderable reduction in the joint spaces, and there is some irregularity of the heads and bases of the phalanges. The most typical feature is the subluxation. The lesions are faintly more active in the soft tissues than in the joint itself; jaws negative. Diagnosis, infectious arthritis.

Nonspecific Protein Record.—This patient always reacted violently, with chill, fever, sweating and pain. He received ten injections (Fig. 3). There was no permanent improvement in the case. There was marked immediate improvement following the first injections. The bedside notes on this case may be of interest because of the marked reaction, with slight blood changes which, however, were otherwise characteristic.

Bedside Notes.—Jan. 30, 1918. The patient was injected yesterday with 1 billion typhoid bacillus intravenously at 10:30. He showed no reaction until 11:30, when quite a violent chill began. This lasted for about twenty-five minutes. At the end of this time the chill stopped; patient still complaining of being cold. This lasted for about an hour. At the end of this time he began sweating profusely. Patient's temperature began to rise a half hour after the injection, but did not rise markedly until five hours after the injection. At ten hours after the injection he reached his maximum temperature 103.8 F. A peculiarity of the leukocyte count was seen. The patient had been running a count between 8 and 9,000 in his control. Immediately after the injection

he showed a leukopenia, and four hours afterward he was back to normal again. Since then his counts have been about 1,000 below normal.

Jan. 31, 1918. The patient's fingers and toes are distinctly more flexible. He makes a fairly good fist and stiffness of the fingers before the injection has given place to distinct relaxation. He was unable to move the toes before the injection, and this morning all of the toes on the left foot move very perceptibly, while those on the right foot move more. There is little if any pain in the fingers, but there is still pain in the toes.

Feb. 1, 1918. The second injection was given at 10:30 a. m. The patient had no breakfast; 1 billion typhoid vaccine. At 11 o'clock pulse was fuller, more rapid, regular; at 11:35 patient began to feel chilly. At 11:40 patient

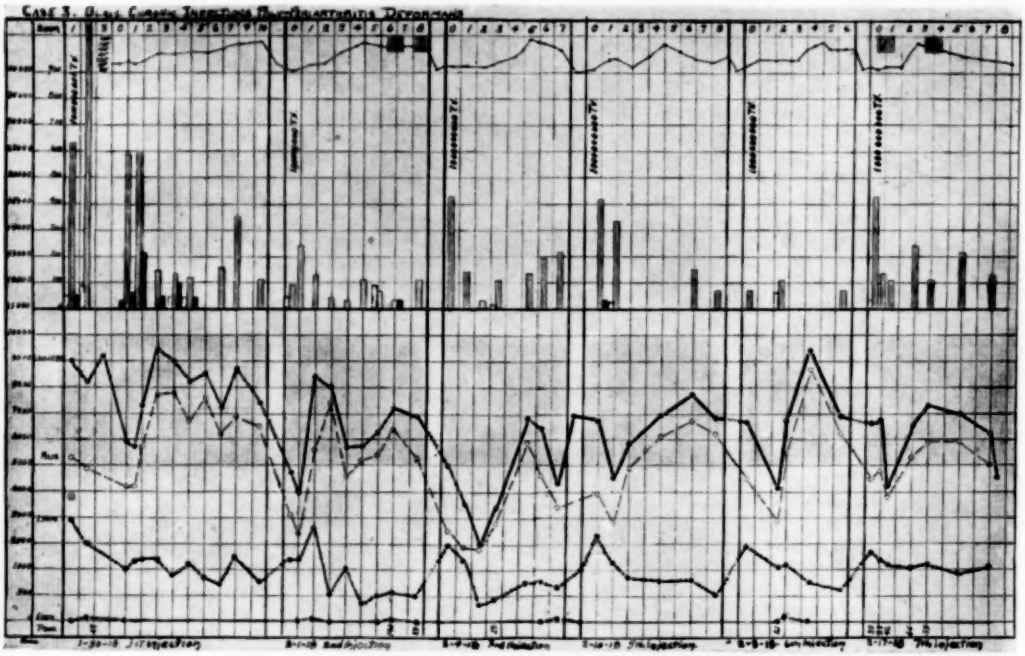

Fig. 3.—Case 3, Blais. Chronic infectious polyarthritis deformans.

was shaking severely and the skin was dry. At 12 patient shaking slightly, at 12:05 chill stopped. The chill lasted for half an hour. Patient now fell asleep. Twenty minutes after the chill stopped patient went into a profuse sweat which lasted for an hour and a half and he complained of feeling hot, much more than at the first injection. This was after the sweat was over, and the skin did not feel particularly moist. This morning there is no question but that the fingers and toes are much more flexible. The patient speaks of this himself. The pain is less marked. The highest temperature was 103.8 F.

Feb. 4, 1918. The patient was seen this morning and complained more of pain than he had at any time since the injection. He has a little more difficulty than was experienced two days ago in flexing the forearm.

Feb. 5, 1918. Patient himself says he is very much better this morning. He makes almost a complete fist with both hands and moves the toes of both

feet, and the feet are very much better. He straightens his knees some better and flexes them fairly well, but the improvement is not so marked in these joints.

Feb. 6, 1918. He does not make quite so good a fist this morning; says his toes and his knees are better. Says his toes are as good as they ever were. He has stiffness in his hands and elbows.

Feb. 7, 1918. Preceding the injection the patient was unable to move his right arm any more than at the beginning; he could not move his left arm. The injection was given at 11:30; dosage 1 billion. The patient reacted by a chill; his temperature went to 104.8 F.

Feb. 8, 1918. Patient is able to move his right arm very freely in all directions. He makes a good fist in both hands. He says the pain in his arms is not in the joint but in the "muscles." The toes are moved freely; hands same. Patient is able to straighten his knees completely.

Feb. 11, 1918. Patient received his fifth injection yesterday. He feels worse this morning; has great difficulty in making a fist. The fingers are stiff; pain in both arms; is unable to straighten his knees.

Feb. 13, 1918. Examination before the sixth injection: The fingers of the right hand are greatly distorted. Patient is unable to flex or extend his fingers completely. Right elbow very sore and movement limited. Fingers of the left hand are extended straight and when flexed lack 2 cm. of reaching abductor pollicis muscle. The left elbow extends the same as the other, but flexion is more equal on either side; is able to extend right knee better than the left. He has movement of the toes.

Following the injection: Patient has noticed a slight improvement, as in previous injections. The chill was less severe than the previous one but he continued perspiring through the night. He is able to close the fingers of the right hand with effort (which he could not do before the injection). The right elbow seems less sore today. The left hand shows slight improvement in flexion of the fingers—within 1 cm. of adductor pollicis.

Feb. 17, 1918. Patient was given seventh intravenous injection today. He had a chilly sensation during the day but no severe chills. Perspiration was very profuse and continued well into the night. The pyrogenic reaction was marked.

Feb. 21, 1918. Patient is in a miserable condition this morning, as bad as at any time since entering the hospital. His wrists are swollen and he cannot close his fingers, and he moves the right arm only slightly and with considerable pain. His knees and toes are practicably immobile. There are no heart murmurs. The rhythm is regular. Because of the discomfort to the patient, further examination could not be satisfactorily carried out.

Feb. 28, 1918. Practically no beneficial results were obtained from the use of typhoid vaccine.

CASE 4.—*Multiple periarthritis deformans and chronic arthritis.*

History.—Shag. Indian girl, aged 12, entered the orthopedic department of the University Hospital because of multiple joint deformities. Transferred to the pediatric department Feb. 24, 1918, for examination and nonspecific protein therapy. Family history, very indefinite.

Past History.—Patient had never been able to walk; said she used to crawl on hands and knees, later used a wheel chair. She said her condition was the same at the time of examination as it had always been; had become neither better nor worse. She never went to school; was able to write some, but could not read. She had not had measles, chickenpox or smallpox, but had had mumps.

The patient had been living with her aunt. She insisted that the vaginal discharge had always been present. There was no burning urination or other symptom. Patient had a tendency to constipation; no nocturia; appetite was good.

Orthopedic Record.—Patient entered the orthopedic ward Oct. 27, 1917, as an emergency state case. No definite history obtained. The lower and upper extremities were deformed, due to arthritic process in the elbows, wrist, fingers, hip, knees, ankles and toes. The right hip was completely ankylosed, the left partially. The knee joints were both hypertrophied, while the surrounding muscular tissue was atrophied. The toes on either foot were deformed, producing hallus valgus deformity of both large toes. Several other toes were of the hammer type. There was ulnar flexion deformity of the fingers. The fingers showed hypertrophic joints and Heberden's nodes. The elbow joints were partially ankylosed so that the forearm could not be fully extended. On the posterior surface of either elbow were bursae, possibly due to the fact that the child had been compelled to creep on the forearms and knees. The

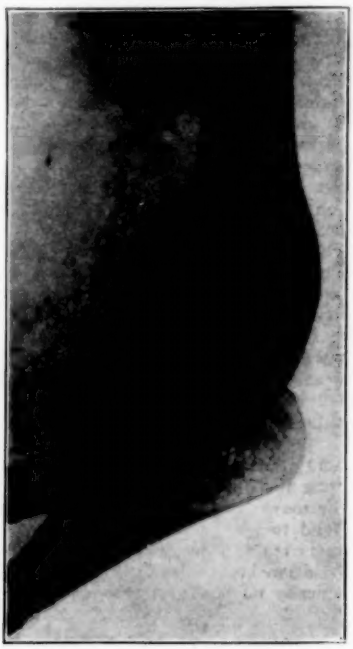

Fig. 4.—Case 4. Elbow showing the absence of epiphyses.

reflexes were normal; tonsils were enlarged; teeth in fair condition; lungs negative; heart negative.

Roentgen Report.—Stereogram of the pelvis and hips. The pelvis is irregularly deformed. There appears to be complete ankylosis of the left hip, while the right is not entirely ankylosed. There remains a plane of separation between the flat head of the femur and the acetabulum. The lesser trochanters are enormously enlarged. The femurs are hyperplastic. There seems to be ankylosis of the lower lumbars and no epiphyses are seen. Stereogram of elbow (Fig. 4) shows similar changes. This is not a true ankylosis but a marked deformity of the articular surfaces. The joint surface is V-shaped and the bony trabeculae are unusually distinct. No epiphyses. There is evidently some gross anomaly in development. We are unable to conceive of these changes as the result of an inflammation. Diagnosis impossible.

Nonspecific Protein Therapy.—This patient received ten intravenous injections of typhoid vaccine. Each one was followed by a typical clinical reaction (Fig. 5). The patient felt so much better after each reaction that she begged for the next. She was always more supple and generally more comfortable. The patient made undoubted improvement. The joints were more relaxed; she moved about remarkably well in her bed, a thing she could not do before

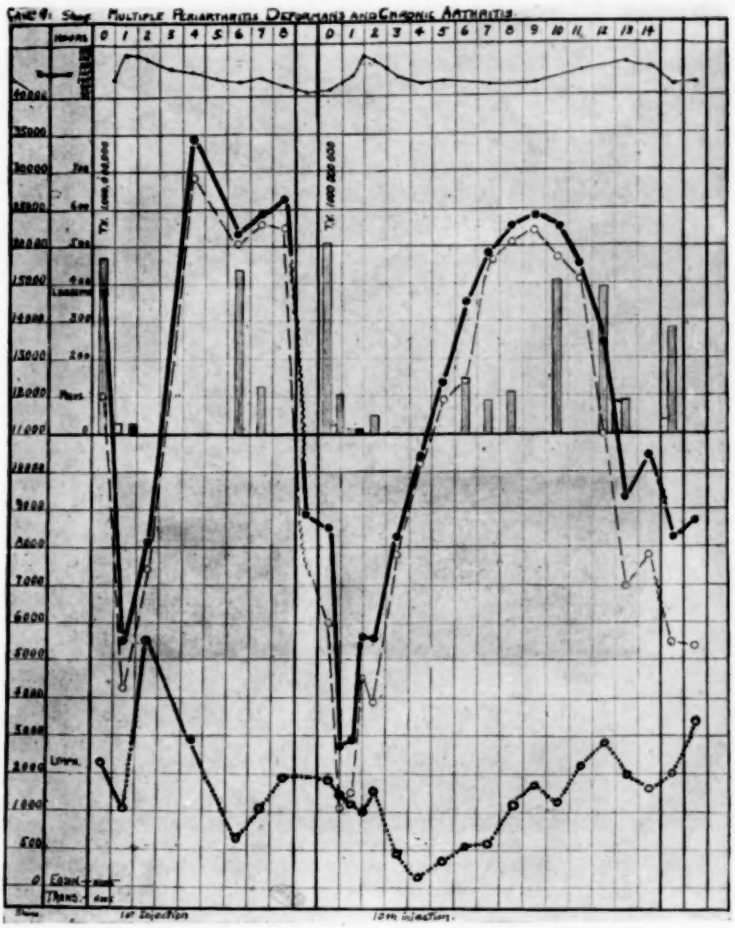

Fig. 5.—Case 4. Shag. Multiple periarthritis deformans and chronic arthritis.

the treatment. She learned to knit and to wheel herself about the ward in a wheel chair. The structural bony changes were unaltered, but the joint stiffness was very much less marked. No perceptible change was noted in the vaginal discharge, which was still fairly profuse and of a whitish, catarrhal character. No gonococci were found on repeated examination. The reactions recorded are the first and tenth.

CASE 5.—*Acute rheumatism; joint swelling; no structural change.*

History.—Miss W., a nurse, aged 22, was admitted to the medical ward of the University Hospital Jan. 29, 1917, complaining of swollen and painful knees. In 1914, she had a severe attack of quincy, lasting for four weeks. The abscesses were not lanced. Since that time she had had frequent sore throats. In December, 1916, she had a severe attack of tonsillitis with fever for three days. Following her recovery she was well until Jan. 22, 1917, when her back became lame. On the 23d there was some pain in the left knee. The right

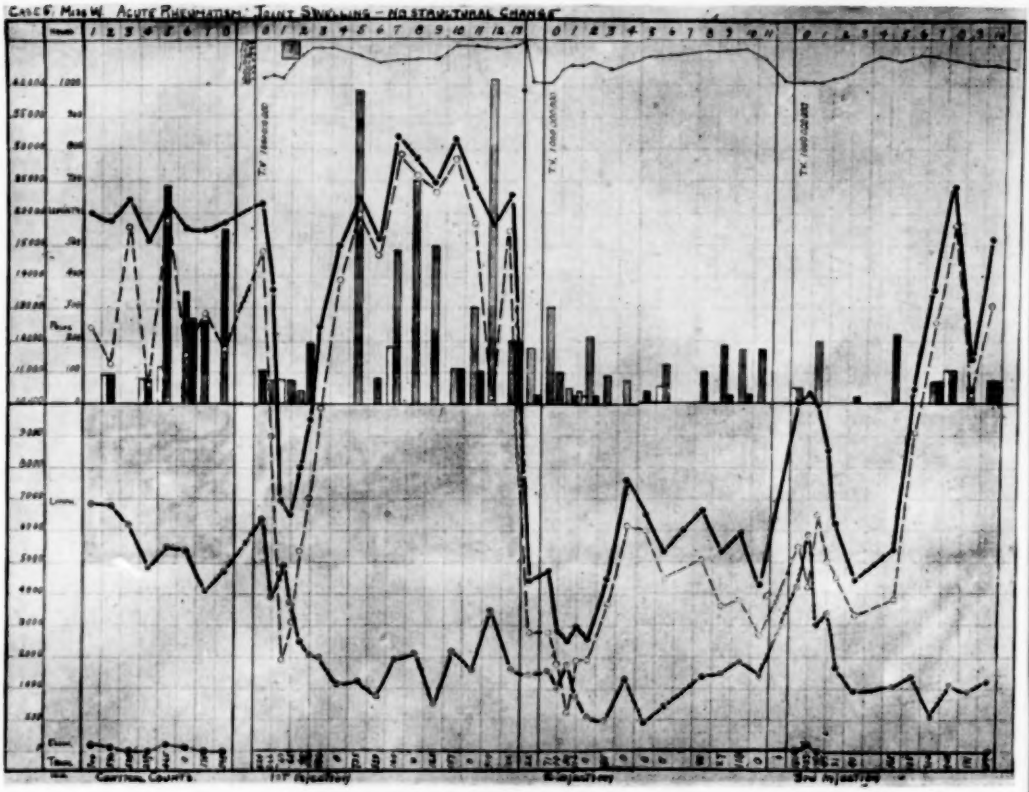

Fig. 6.—Case 5. Miss W. Acute rheumatism; joint swelling; no structural change.

knee was involved the following day. On examination both knees were swollen and tender but not reddened, and no fluid was demonstrable. There was slight swelling of the right ankle. The joints were warm and sweating. The tonsils were enlarged and septic. There were no heart murmurs. The patient was put to bed with the joints wrapped in cotton and given sodium salicylate, 160 grains per day. There was marked improvement under the salicylate treatment, and on Feb. 10, 1917, she was sent home to return for a tonsillectomy in several weeks. The last of March, 1917, the patient had her tonsils removed and six weeks later she had a slight attack of arthritis which cleared up in

a week under sodium salicylate, 150 grains per day. From that time until December 21 she was well and gained 40 pounds. December 21, following a severe head cold, she developed pains in her joints. The joints involved were the knees, hips and elbows. Just before the attack of cold she noted that she had dyspnea and some pain at the base of the heart. Examination on entrance showed a definite mitral insufficiency and a murmur at the base in the pulmonic area, probably functional. Roentgenogram of the teeth was negative; of the sinuses, showed normal frontals, increased density in the right posterior ethmoid and a hazy, indefinite density in the right antrum, without changes in the bony wall. She was treated with salicylates and oil of wintergreen applied to the joints. She did not make satisfactory improvement, and Dec. 29, 1917, she was transferred to us for nonspecific protein treatment. On the day of the injection she was complaining of soreness and stiffness in the elbows and knees.

History of Present Attack.—December 6, patient reported a cold, headache, sore throat and general aching of the body. Temperature at 4 a. m., 100.4 F. Culture taken was negative. She returned to duty. December 22 she was unable to report for duty because of painful swelling of the knees. She was unable to walk. She made no satisfactory improvement on salicylate. No further foci could be found, and, for this reason, she was transferred to this department. The day of the first injection the patient was still complaining of soreness and stiffness in her joints, elbows and knees.

Jan. 22, 1918, the following note was made: "Left border of the heart is 10 cm. from the midline; right border 2½ cm. Apex is felt in the fifth intercostal space, nipple line. Upper border is, apparently, on the third rib. Careful palpation reveals no thrills. The heart impulse is not marked. A double murmur is heard at the apex, giving the sensation of distance. Both sounds are heard. The murmur, particularly the systolic, is heard in the axilla. The diastolic murmur becomes louder toward the sternum, and is very loud and exhaustlike at the pulmonic area. The pulmonic second sound is definitely accentuated, and is not to any degree displaced by the loud murmur in the pulmonic area. The diastolic murmur can be heard all over the precordia. The patient is very much better after her last injection."

Roentgen Report.—Roentgenogram of the teeth negative; roentgenogram of the sinuses shows normal frontals, increased density in the right posterior ethmoids and a hazy, indefinite density in the right antrum without changes in the bony wall. Diagnosis, posterior ethmoiditis. Stereogram of the knee, good rays. These plates show the bones normal in outline, density, texture and relationship. We see no evidence of involvement of the bones or cartilages; a soft tissue lesion.

Nonspecific Protein Therapy Record.—This patient was given three intravenous injections of typhoid vaccine, 1 billion each, December 29, January 1 and January 18. The individual reactions are recorded in Figure 6. The patient's symptoms were some better after the first injection, and disappeared entirely after the second. Because of her heart condition she was allowed to be up only two or three hours a day until the 16th when she was up considerable. On the 18th she complained of being uncomfortable and unable to move her lower extremities. Six hours after the last food she was given her third injection This cleared her symptoms up completely within twenty-four hours There had been no return to date, May 21, 1918.

CASE 6.—*Hypertrophic arthritis.*

History.—Miss Wor., aged 22, stenographer, entered the University Hospital in the medical clinic complaining of swollen and painful joints and inability to walk.

Family History.—Mother had rheumatism and a chronic heart lesion.

Present Illness.—Began four years before admission with a gradual onset; first, there was sharp pain in the left hip and thigh, then in the right knee.

Four days later the metacarpal-phalangeal joints were involved. Joints in the hands and fingers had been painful for three years; the ankles were affected one year prior to admission and since then she had had difficulty in walking. The past three weeks the jaw had been involved.

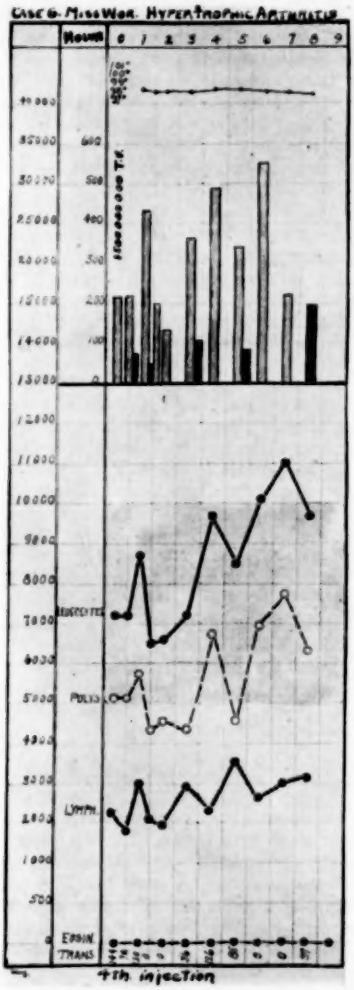

Fig. 7.—Case 6. Miss Wor. Hypertrophic arthritis.

Examination.—Patient was of moderate build with good musculature. The apex of the heart was in the fourth intercostal space and the sounds were clear and distinct, with no murmurs. The extremities showed hypertrophy of all the joints, especially the ankles and finger joints. There was beginning ulnar flexion of the latter. The picture was typical of hypertrophic arthritis.

Nonspecific Protein Therapy Record.—The patient did not improve under salicylates and no focus of infection being found she was given 300,000,000 typhoid vaccine Dec. 10, 1917, at 1:25 p. m. This was followed by a chill beginning at 2 and lasting for twenty minutes; the temperature rose gradually, reaching a maximum of 100.8 F. at 5 p. m. There were no focal symptoms accompanying the reactions. The patient thought the knees and ankles were more flexible.

Dec. 17, 1917. Patient was given two injections of 500,000,000 and 1 billion typhoid vaccine with the same reactions as the first. Dec. 19, 1917, she was given agar agar intravenously. Two minutes after the injection the patient complained of feeling queer, with tickling and choking sensations in the throat and tingling in the feet. She was extremely cyanotic, with an anxious expression. The pulse was small, weak and rapid. Her condition resembled shock. In fifteen minutes she felt better, but the cyanosis was still present. In one hour her condition was normal.

Jan. 7, 1918, she was transferred to us for intravenous typhoid vaccine. She was given a dose of 1½ billion. Her temperature rose to 102.4 F., and was preceded by chill (Fig. 7). Her joint condition showed no permanent improvement after these four injections of typhoid vaccine, so she was returned to the medical department where subsequently she received three doses of Colles' serum. These injections gave a severe symptomatic reaction, but the temperature never rose above 102.2 F. After three injections she was markedly improved and able to walk.

CASE 7.—*Atrophic arthritis.*

History.—Mrs. McD., aged 64, entered the Cowie Hospital Oct. 18, 1917, complaining of pain in the knees and difficulty in walking. Duration, four and a half years.

Five years prior to admission the patient had gastric ulcer with hemorrhage from the stomach. Six months later there was a second hemorrhage, and since that time there had been pain in her knees which gradually became worse. Both knees were affected. They were swollen, and it was impossible completely to extend them. The pain was more severe on walking. No other joints were affected. At 14 the patient had a severe attack of inflammatory rheumatism lasting three weeks. The left side and knee were involved. Recovered with a heart lesion which was perfectly compensated. Had never had any trouble with her tonsils. Except for a tooth removed recently which had a small pus pocket at the root, there had been no trouble with her teeth. In March, 1917, the patient had a severe attack of laryngitis which was followed immediately by "sciatica." Twenty-five years ago the patient was in a railroad accident. Her sternum was fractured (?) and her back was injured, and has been weak ever since. Fifteen years ago she was treated for "catarrh of the stomach." This was the first record of stomach trouble. Seven years ago the patient had ptomain poisoning from oysters, and during the following year she lost 35 pounds. Fifteen months after this attack she had her first hemorrhage of the stomach (March, 1912). The second hemorrhage occurred in November, 1912. For the two years following she was troubled with pain in the epigastrium of a sharp, shooting character, occurring four hours after eating. In the fall of 1917 she had an acute attack of stomach trouble, and at the same time her knees became worse. She had never noticed any tarry stools. Menopause at 50. Had a single severe hemorrhage which was repeated the second month. No other difficulty.

Family History.—A daughter is said to have had gastric ulcer. One son has had medical treatment for gastric ulcer. The patient's mother had severe stomach symptoms and one sister had "gastric ulcer."

Physical Examination.—Large frame. Fairly well developed musculature; muscles soft. Panniculus thick all over the body. Sight edema over both ankles. Inguinal glands just felt; otherwise glands were negative. Circumference of the knee, 44 cm. both sides. Patella reflexes not obtained, probably due to position; elbows prompt.

Lungs: Increased vesicular inspiration all over (moderate degree of emphysema); no other adventitious sounds. Patient had been short of breath for five or six years.

Heart: Apex difficult to locate, apparently the same as the left border—11 cm. from the midsternal line just outside the mammary line. Right border

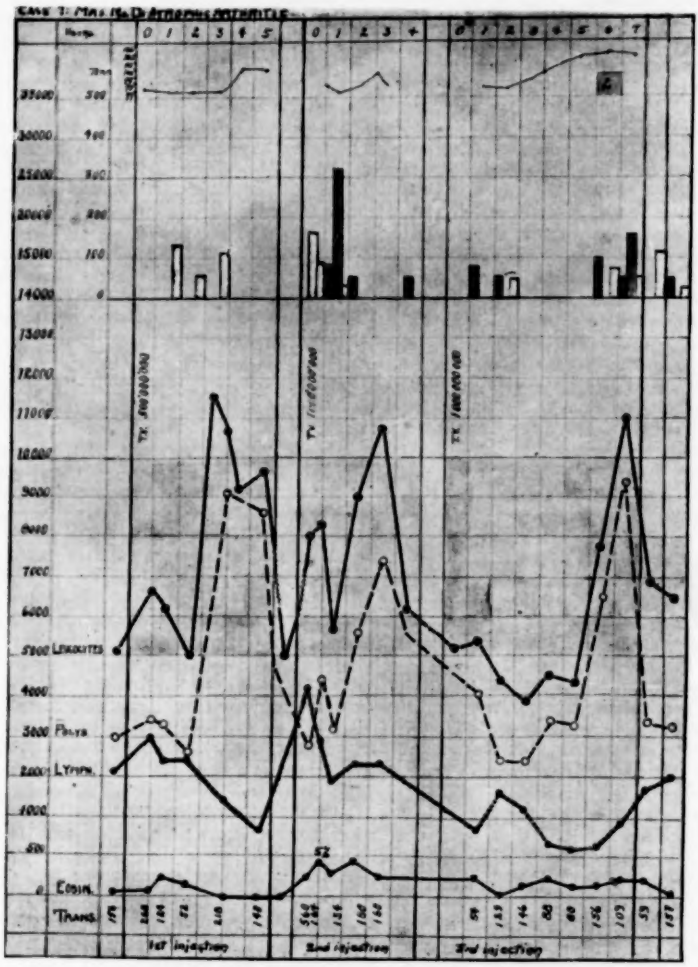

Fig. 8.—Case 7. Mrs. McD. Atrophic arthritis.

2.5 cm. Upper border on third rib. Aortic arch did not seem to be increased. Heart impulse moderate. No thrills. First strike of the apex about normal; it was followed quickly by a very distinct, short, blowing murmur which terminated in a flapping second sound. It was difficult to differentiate whether the murmur followed the first sound and was part of it, or whether it was

part of the second. The murmur was not transmitted to the sternum, was not well transmitted into the axilla, but could be heard. Pulmonary second sound was, possibly, slightly accentuated and louder than aortic second sound. Aortic area seemed to be negative. The first sound in the carotid was very plainly heard, somewhat roughened, but no thrill could be felt on reexamination. Blood Pressure: Systolic, 125; diastolic, 70; pulse pressure, 55. The pulse is regular, 78, fairly easily compressed; felt slightly after compression; not particularly tortuous; negative. The patient had been conscious of the ankle swelling. She had no characteristic pain in the left arm, but complained of some rheumatic pain in the right shoulder. No chest tightness.

Abdomen, negative.

Blood: Red cells, 5,180,000; white, 5,500; hemoglobin, 80 per cent. (Talqvist). Polynuclears, 56; small lymphocytes, 29 per cent.; large lymphocytes, 8.5 per cent.; transitionals, 2.5 per cent.; eosinophils, 1 per cent.; mast cells, 1.5 per cent.

Urine negative

Stomach functions negative.

Roentgenographic Record.—"Lateral stereogram of each knee and an anteroposterior including both knees. The pathology is virtually identical in both knees. Superficially the most striking feature is the marked osteophyte formation at the margins of the articular cartilages, but careful observation demonstrates a marked erosion of these cartilages with lateral luxation. The erosion is most marked over the internal condyle."

"Diagnosis, chronic atrophic arthritis."

Nonspecific Protein Therapy.—Nov. 7, 1917, the patient received the first intravenous injection of typhoid vaccine, dosage, 1 billion. At the end of three hours she had a marked chill and suffered from severe pains localized in the back, legs and knees and an increase in temperature (Fig. 8). November 8, she was given her second intravenous injection. The chill in this reaction was delayed for four hours. It was very severe. The maximum temperature was only 100 F. Pain was very severe. On the 12th she received her third injection; the chill followed in three hours with a rise in temperature to 102.4 F. following it. After the nonspecific protein therapy the soreness disappeared from the knees and they were straighter, although the difficulty in walking still persisted.

Case 8.—*Hypertrophic arthritis of spine.*

History.—Mrs. B., housewife, aged 46, entered Cowie Hospital because of neuralgiform pain, occurring in remittent attacks involving the right leg and thigh and the posterior cervical region. Family history negative.

Past History.—The attacks of pain were present for eight or nine years, the first attack lasting a year. At this time she had sharp shooting pains in the chest and soreness in the left arm. There had been remissions lasting a year or more when she had felt normal. For the previous two years the pain had been localized during the attacks in the right leg and hip and in the back of the head and neck. There was pain and soreness on pressure which was aggravated by walking or standing. Because of the pain she found it difficult to stoop over.

At the age of 18 she had an infected fallopian tube with abscess formation. The first child, born about twenty years previously, was delivered by high forceps, and the patient was badly lacerated. In 1913 one ovary, one tube, and the uterus were removed. This operation improved the patient's headaches and she was distinctly better following it. She has always been constipated and believes that the attacks of neuralgiform pain follow a period of constipation.

Physical Examination.—Examination showed a small, well built woman, who looked about 35 years old. Physical examination was negative except for absent pharyngeal reflex, inframammary tenderness, slight tremor of the

extended hands, and tender points along the sciatic nerve, the second, third and fourth cervical vertebrae and the lumbar vertebrae. The heart on Aug. 30, 1916, showed the apex in normal place and the heart sounds negative. In November, 1916, examination showed apex and outlines normal, marked pulsation of the neck with slight thrill and the short soft puff which was not transmitted was heard at the apex. The pulse for this time was 104 F. Aug. 6, 1917, the heart was negative.

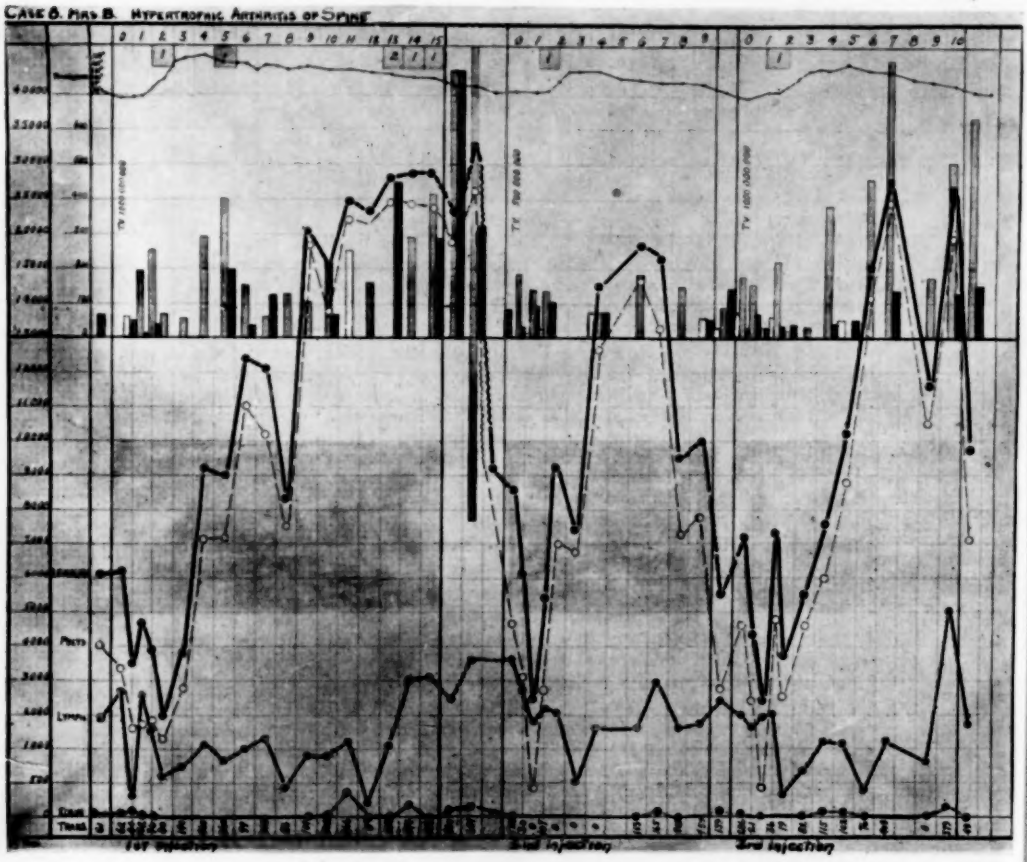

Fig. 9.—Case 8. Mrs. B. Hypertrophic arthritis of spine.

Neurologic examination showed areas of hyperesthesia on the right leg and thigh corresponding to the cutaneous distribution of the first, second, third and fourth lumbar roots and the first sacral. The upper boundary of the hyperesthesia was two finger breadths above the pubes and extended in a curved line to the lower dorsal vertebral spine. The lower limit extended diagonally across in front of the leg, involving a small semicircular area on the inner central aspect of the sole of the foot. There were pain points along the

course of the sciatic nerve. A diagnosis of radiculitis of the lumbosacral plexus was made and a roentgen-ray examination was recommended.

Roentgenographic Report.—A stereogram was made of the lower lumbar and upper sacral region. These were satisfactory roentgenograms, from the third lumbar to the sacrum, including both sacroiliac joints. The spine was straight and the fifth lumbar was of the free standing normal shape. The pathology appears to lie in the anterior or intercentral articulations of the lumbar spine. The findings consist of a roughening and accentuation of the upper and lower surfaces of these centra, with a distinct lipping at the angles. There is also a slight lipping at the lower margin of the iliosacral articulations. The majority of the pathology, however, is in the spine. The hip is negative. This is an anterior spinal arthritis.

Nonspecific Protein Therapy Record.—Feb. 7, 1918, the patient received intravenous injection of typhoid vaccine, dosage 1 billion. Within a half hour she was chilly and complaining of severe headache and backache (Fig. 9). Within three hours her temperature had risen to 104 F.; she was very restless, nauseated, and delirious. Respirations were very short and rapid and she was cyanotic. Because of the severity of the reaction she was given on the second injection, February 11, only 500,000,000 as a dose. This was followed within half an hour by a severe chill and headache; the reaction was completed by 6 o'clock. The temperature did not rise as high as might have been expected from the severity of the chill. February 13, she was given her third and last intravenous injection of 1 billion typhoid vaccine. This was followed by a very severe chill lasting for twenty minutes, a marked increase in temperature and at the end of three hours delirium. She localized the pain in the occipital region, in the back and in the right leg and thigh. During her delirium she complained of having two heads, both of which ached. Temperatures taken showed the axillary temperature to be a degree and a half below the temperature taken in the right popliteal space. The temperature over the back of the neck was perceptibly higher than that of the face. On the day following the injection the patient found that she could stoop over without pain and since that time the spine has remained more flexible. She was told the intravenous injections might arrest the arthritic process but could not repair structural damage already done.

CASE 9.—*Gonorrheal vulvovaginitis.*

History.—Frances C., a girl, aged 2, entered the pediatric department, Jan. 4, 1918, because of profuse vaginal discharge.

Family History.—The mother denied vaginal discharge in herself and other little girl.

History.—Has no bearing on the case.

Present Illness.—This started four weeks prior to admission; yellow white vaginal discharge; genitals excoriated and red, causing much pain on micturition. Smear positive for gonorrhea.

Physical Examination.—General examination negative.

Genitals: There was a very slight excoriation of the external parts; marked vaginal discharge of yellowish white pus. Anus normal and clean.

Vaginal smear positive. Wassermann negative. Neisser complement fixation positive Jan. 7, 1918. Neisser complement fixation negative Jan. 25, 1918.

Nonspecific Therapy Report.—This patient received five intravenous injections of typhoid vaccine; seven partly intravenous and partly intramuscular. With the exception of the final dose of 500,000,000, the dosage was one billion. The injections were given January 9, 12, *19*, 25, 28, and February 1, *4, 7, 9, 11, 13, 17.* Those in italics were partly intravenous and partly intramuscular. It was almost impossible to get a vein in this child. Most of the intravenous injections were given into the jugular. Marked leukocytic reactions followed each injection in which counts were made excepting the fifth recorded. The

temperature reaction was not marked; 102 F. recorded only once. The patient suffered no inconvenience whatever from the injection (Fig. 10).

There was no lessening of the vaginal discharge following the first injection. After the third injection the nurse was certain the discharge was distinctly less, but it still had to be charted profuse (3). After the sixth injection the discharge was distinctly less, now charted (2).

Two days later very little discharge could be obtained for a smear; only a few leukocytes and a few epithelial cells were present and a few intracellular cocci. After the ninth injection the discharge was still slight in amount and from then on there was very little visible discharge. The case at the time

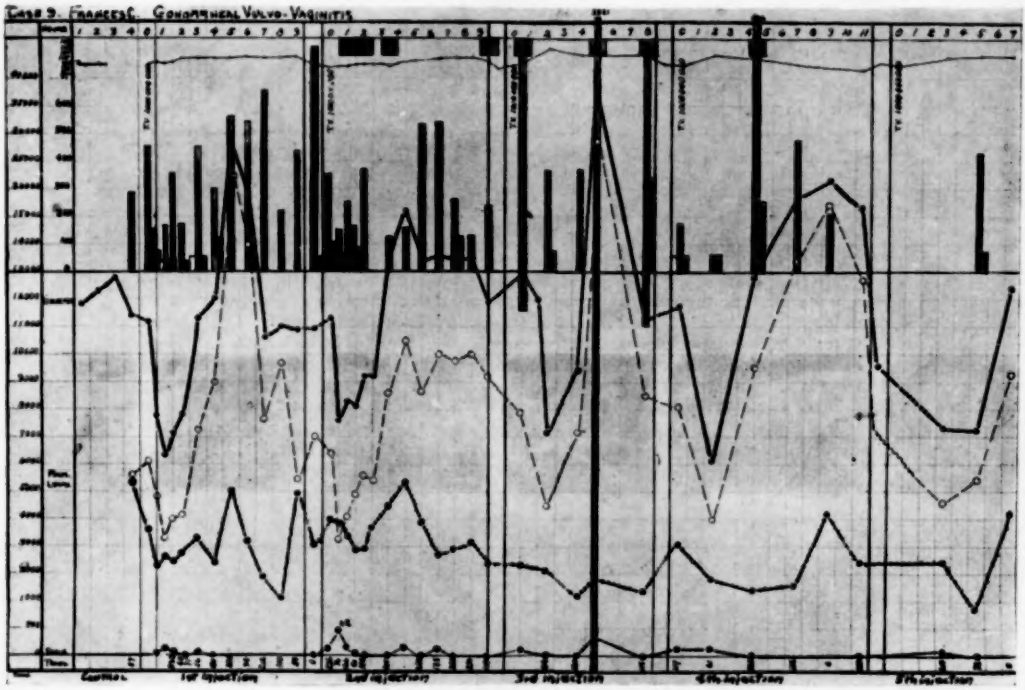

Fig. 10.—Case 9. Frances C. Gonorrheal vulvovaginitis.

of the report was practically clear without any further treatment. (Note.—July 1, patient continued to have a slight discharge and occasionally intracellular organisms were found.)

Case 10.—*Suppurative mastoiditis with chronic pulmonary tuberculosis.*

History.—Frei., a schoolboy, aged 9. The patient came to the University Hospital Oct. 17, 1917, because of double discharging ears. The temperature was normal. A double mastoid operation performed Oct. 18, 1917. The patient reacted well. There was a slight temperature reaction after the operation, but this subsided on the 21st and remained normal until the 28th, from which time until November 5, when he was referred to the pediatric department, it varied from 100 to 102 F. Aside from the discharging ears our examination at this time was negative.

Examination.—November 4, the patient was referred to us because of continued elevation of temperature ranging from 100 to 102 F. in the afternoon, returning to 99 in the morning. At this time we were unable to find any definite signs in the heart and lungs. Lumbar puncture gave clear fluid under increased pressure; about 20 c.c. came away. Total cells 650, all lymphocytes. Nonne, Noguchi, alcohol and Fehling tests negative. The blood pressure was found to be negative.

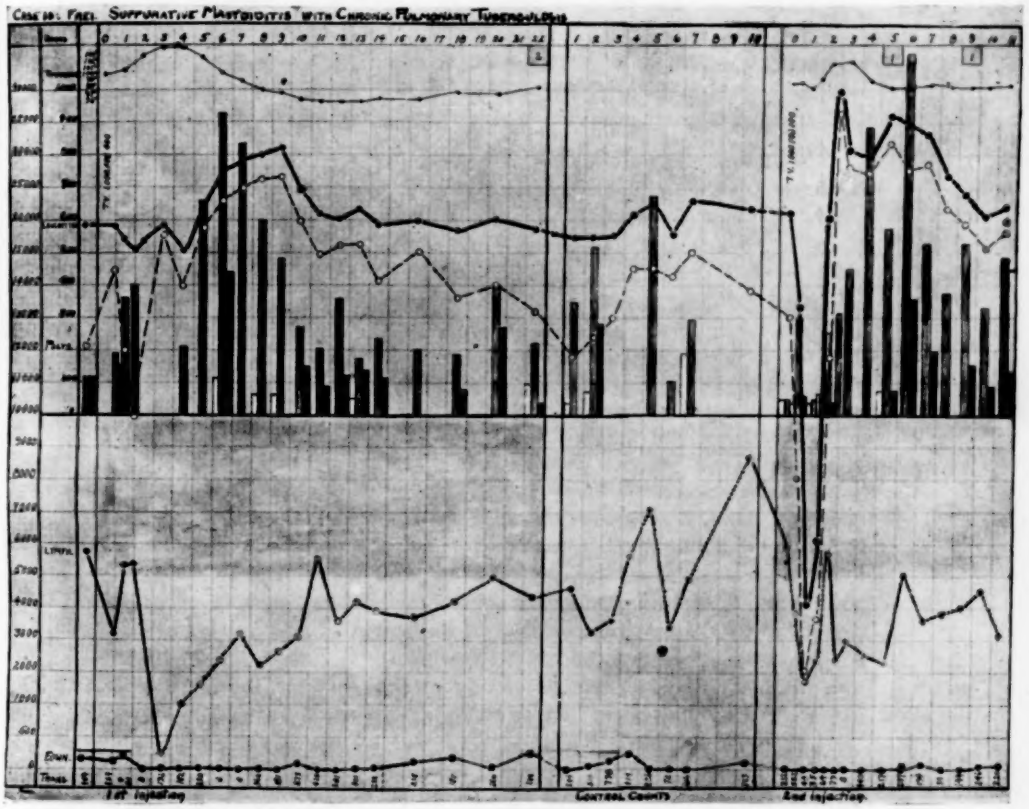

Fig. 11.—Case 10. Frei. Suppurative mastoiditis with chronic pulmonary tuberculosis.

December 13, referred again; at this time the heart was 3.5 by 8 cm. Roentgen ray showed cardiac enlargement over previous plate. Sounds negative; no murmur. Lungs: Low down in the right axilla there was slightly impaired resonance; exaggerated vesicular breathing, an occasional râle. Dulness in the right back below the angle of the scapula; bronchovesicular breathing over this area; increased whispered voice. Many râles. From now on definite chest signs were always present. A diagnosis of pulmonary tuberculosis was made on the physical finding of tubercle bacilli and by the roentgenogram.

This case was selected because of the suppurating mastoid, to see if any effect could be produced on the discharge, and to determine what effect the typhoid vaccine (intravenous injection) would have on the blood in this condition associated with tuberculosis.

Nonspecific Protein Therapy Record.—A first injection of 500,000,000 typhoid vaccine was given Dec. 21, 1917. It was followed by a chilly sensation at the end of one hour and nausea at the end of three hours. The temperature rose to its maximum of 105.4 F. three hours post-injection (Fig. 11).

The second injection was given Jan. 1, 1918, at 7:30 a. m.; the dosage was 1 billion; this was followed in two and one-half hours by a slight chill.

Two days after the injection the discharge from the ears had practically ceased, and a week later the department of otology found no discharge when the wound was dressed. The process was chronic and of three months' duration.

MOVEMENT OF NORMAL CELLS INDUCED BY FOREIGN PROTEIN

The Leukocytes.—Following an injection of typhoid protein there is almost invariably a decrease in the total leukocyte count. Commonly this decrease amounts to a distinct and often to marked leukopenia, but not always. In Cases 6 and 9, the leukocytes never went below normal. In Cases 1, 3, 4, 5, 7 and 10 the leukocytes did not go below normal until the second or third injection. This decrease in the leukocyte count in our cases varied from 1,600 in Case 6 to 16,000 in Case 10. The leukopenia usually immediately follows the injection. In twenty-nine reactions it occurred at the following hours.

Hours	½	1	1½	2	2½	3	Total
Number of Reactions	2	11	5	7	0	4	29

A reversal occurred in five cases (4, 5, 7, 8, 9). Following the leukopenia there is always a rise in the leukocytes. This occurs whether the leukocytic movement is above or within the normal limits. The leukopenia in the four children studied was not as low as in the adult cases, 5,000 being the lowest count. The greatest upward excursion from the lowest point reached to the height of the reaction was 33,000. The highest induced leukocytosis above the control was 29,000. The height of the leukocytes is usually reached in from four to nine hours after the injection. In twenty-nine reactions the height was reached at the following hours:

Hours	1½	2½	3	4	5	6	7	8	9	10	11	12	15
Reactions	1	2	3	5	3	2	7	2	3				1

In one case, No. 8, the last observation was made at the fifteenth hour, but the reaction continued throughout the next two days, when it reached its height, 35,000. By reference to the charts it will be observed that intercurrent drops or pseudocrises may appear in the leukocyte curve. The movement downward may be as great as 4,300 (Case 8). One might thus be easily misled and think the leukocytic reaction was over when, as in this case, the most marked changes were to come many hours later — numerous myelocytes, atypical cells

and nucleated reds. The end of the leukocytic reaction is usually characterized by a critical fall.

Influence of Size of Dose on the Reaction.—On three occasions a 500,000,000 dose was given. In two of these the reaction was distinctly less marked; in one, a first injection, the reaction was the greatest. We have observed this many times in the simple clinical reaction, and at times when accidentally only part of the injection went into the vein.

The Polymorphonuclears.—The polymorphonuclears generally follow the total leukocyte curves pretty closely (Figs. 1, 5, 6, 9, 11), excepting at the time of the leukopenia, when there is very frequently a reversal. This reversal always precedes a prompt rise in the leukocytes (Figs. 5, 6, 8, 9, 10). The polymorphonuclears induced by the injection of the foreign protein took the nuclear stain after the fashion of new cells, as shown by the chromatin network staining very distinctly. Our attention was frequently called to the large size of the nucleus. We have not as yet made any Arneth counts. This question is of interest because of the shift to the left in typhoid fever.

The Lymphocytes.—In all cases, except Case 9, the large lymphocytes almost invariably disappear from the blood at some time during each reaction. The small lymphocytes, on the other hand, never completely disappear. There seems to be no relationship between the appearance of atypical large lymphocytes and the disappearance of the normal large lymphocytes; for example, in Case 3, first reaction, the relation of atypical large lymphocytes to the normal lymphocyte is as follows:

Hour	1	2	3	4	5	6	7	8
Normal	28	0	90	40	85	71	44	0
Atypicals	52	94	45	40	0	142	131	37

In four cases (1, 3, 7, 8) the number of large lymphocytes at times exceeded the number of small lymphocytes. In three of these cases (1, 3, 7) this reversal of the normal relationship does not occur until after the first injection. In Case 8 it occurs late in the first reaction. Delany,[6] and also Krause,[7] found the large lymphocytes equalled or exceeded the small lymphocytes in a differential count of malarial blood. This was so constantly present that Delany considered it as diagnostic as finding the plasmodium.

The total lymphocyte count in normal blood ranges between 1,500 and 2,200 per c.mm. Following an injection of typhoid protein there is almost invariably a decrease in the total lymphocyte count, almost immediately after the injections. This may only be slight, but the

6. Delany: Brit. M. J., March 28, 1903.
7. Krause, W.: J. A. M. A., **43**:1202, 1904.

movement downward is nevertheless present. There is one exception, Case 3, reaction 1. Out of 29 reactions a lymphopenia occurred in 24. The lowest recorded is 200 (Case 4, second reaction). There were 10 reactions below 500 in 6 cases (1, 3, 4, 5, 8, 10). A lymphocytosis occurred in 21 reactions out of the 29; of these only 9 rose above the initial count. The highest lymphocytosis initiated by the injection was 8,800 and occurred during the interval between the first and second injections in Case 10. This patient had pulmonary tuberculosis and had an initial lymphocytosis of 5,800. In 7 cases (1, 3, 4, 5, 8, 9, 10) there was a lymphocytosis in the control, varying from 2,800 to 5,800. In 15 reactions the final lymphocyte count was lower than the initial count preceding the injection.

A decrease in the number of lymphocytes followed the chill in 23 out of the 29 reactions. This occurred in all the reactions in children. In no case do we get the immediate rise following the chill. This calls to mind the work of Rause on struggle lymphocytosis in which we have been interested. In dogs during marked struggle he found an increase in the lymphocytes. The chills in some of our reactions were so violent that we were looking for a similar increase in the lymphocytes, but it did not occur.

The Transitionals.—The total number of transitionals in normal blood ranges between 230 and 380, 3 per cent. and 5 per cent. In twenty-five reactions the transitionals ran below the normal; four of these showed an initial low count. In thirteen reactions the transitional count was above normal, two of them having an initial high count. The highest count is 866—3.5 per cent.

The Eosinophils.—In two cases only did the eosinophils show an increase, and this increase was only slight — Case 7, second reaction, 5 per cent., or a total of 400 cells; Case 9, second reaction, 6 per cent., or a total of 450 cells. The eosinophils, indeed, were conspicuous by their absence. This is strong proof that the reaction is not of an anaphylactic nature. In Cases 7 and 9 the increase came, in each case one-half hour after the second injection, suggesting an anaphylactic response to the previous injection. In Cases 3 and 5 they were present in the control and almost invariably absent during the reaction.

OCCURRENCE OF ABNORMAL CELLS

The Myelocytes.—Myelocytes were quite regularly found after the injection, twenty-four out of twenty-nine reactions. They were rarely present in the controls. In one case (8) a total of 800 cells were found. The basophil myelocyte was most frequently encountered. Myelocytes most frequently made their first appearance very soon after the injec-

tion, in from one-half to one hour. Of the twenty-four reactions in which they occurred they appeared at the following hours.

Hours after Injection..	1½	1	1½	2	3	4	5	6	7	10	Total
Reactions	1	10	2	3	0	3	2	0	2	1	24

The Nucleated Red Cells.—Nucleated red cells were found in seven out of the ten cases; both megaloblasts and normoblasts were found. Their appearance was not necessarily associated with the appearance of myelocytes. This is interesting in view of Stockard's[8] conclusion that "vascular endothelium erythrocytes and leukocytes though arising from mesenchyme are really polphyletic, each with a different mesenchymal fundament or anlage, and if one is destroyed the others cannot replace it." That is, if the fundament producing myelocytes is destroyed, nucleated reds may still be manufactured but the myelocytic function can never be recovered. That the nucleated reds do not necessarily appear at the same time as the myelocytes might lead one to argue that the same stimulus reacts differently on two different "fundaments."

The Platelets.—We have been impressed with the large number of platelets present in the reaction smears. We were unable to make systematic counts. The morphology of these bodies was frequently quite remarkable;[9] large sized well preserved ones were quite numerous. In Case 7 the plates were at times from one-half to two-thirds the diameter of the red corpuscles with distinct collections of nuclear matter, and at times a reticulated cytoplasm. Similar platelets were seen in several other cases.

Very early in the reaction we observed a stage when it was difficult to obtain a complete count from a single stab of the finger, owing probably to increased coagulation time (Cases 1 and 8 particularly).

Duke[10] has observed after the administration of small doses of typhoid vaccine an increase in the number of the platelets; after large doses, a fall in the curve or a rise followed by a fall. In a typhoid innoculation he believes the effect is irritant (increase) and a toxic dose is not reached, while in typhoid fever the irritant dose is exceeded and a reduced count is the rule.

The Spectroscope.—Early in our work we became impressed with the cyanotic appearance in some cases and particularly a darker appearance in the blood when drawn into the pipet. This was most marked in Cases 7 and 8. In Case 6 intense cyanosis followed an intravenous injection of agar agar. This suggested the advisability of spectroscopic examination to detect the presence or absence of reduced hemoglobin.

8. Stockard: Am. J. Anat., **18**: 1915.

9. Similar platelets have been described by Kemp, Harris and Calhoun. Brit. M. J., Dec. 22, 1906, and Am. J. Physiol., February, 1904.

10. Duke: J. A. M. A., **65**:1600, 1916.

In Case 1, spectroscopic examinations were made with each count. Two bands of oxyhemoglobin were present at all times. In Case 8, the result was the same. In this case the blood looked dark, but this was not due to reduced hemoglobin. In Case 1 the blood never looked dark.

THE ATYPICAL CELLS

Atypical cells almost constantly appeared in the blood stream very soon after the injection of the foreign protein. They commonly continued throughout the reaction. They consisted largely of atypical large lymphocyte forms, and many small lymphocyte forms. In addition to these atypical cells, abnormal cell forms were frequently encountered, myelocytes, and nucleated reds both normoblasts and megaloblasts. Most of these forms are illustrated in the colored plates (Figs. 12 and 13). In Figure 12 Turck irritation forms, changes in the small lymphocyte group, are shown on the first and second lines. Granular, reticulated and multinucleated forms of the small lymphocyte group appear on lines three, four and five. Irregular nucleated and granular large lymphocytes are shown on lines six and seven and in Figure 13.

The Turck irritation forms are usually only found in pathologic blood, inflammatory processes, during or following a leukocytosis. They were only found preceding the first injection; that is, in the first control, before any foreign protein had been injected, in two cases (4 and 9). The former patient had an active gonorrhea, the latter a marked vulvovaginitis in which no gonococci could be found. Both of these patients were children. Four of these eight cases had previously had subcutaneous injections of so-called serum or vaccine. One had typhoid vaccination a year preceding the treatment. These findings would seem to show that an intravenous injection of typhoid protein initiates the appearance of Turck irritation forms.

Acidophil Granular Lymphocyte Forms. — These cells are frequently found in normal blood, but not in large numbers. We have noted two types of these cells. Those with very fine granules and those with large granules sometimes reaching the size of microcytes and not unlike them in appearance. The larger granular forms are the ones charted. Some of these cells show nuclei poor in chromatin and others have a vacuolated protoplasm. Many are binucleated and occasionally a mitotic form is seen. With one exception these forms were never encountered in the control. This patient showed 8 per cent. of the red granular forms in the control, and, in addition to this, there were many of the fine granular forms. The patient had recently been treated with vaccines preceding our investigation.

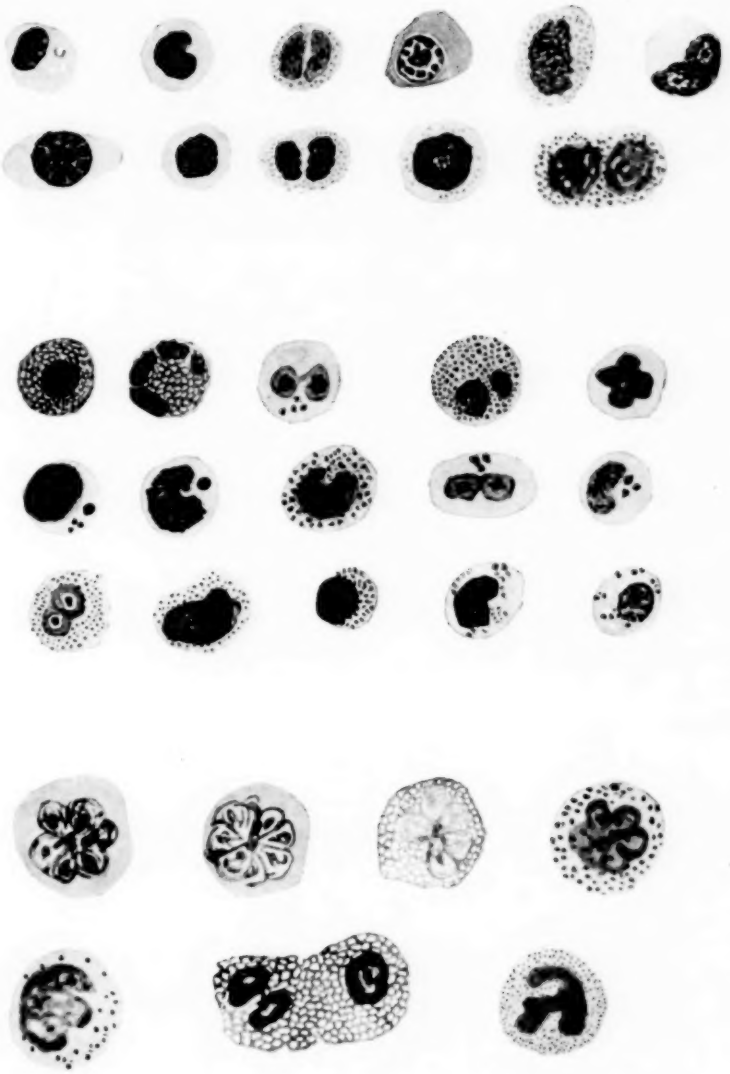

PLATE 1

ATYPICAL WHITE BLOOD CORPUSCLE

ILLUSTRATING ARTICLE BY DAVID MURRAY COWIE, M.D., AND HENRIETTA CALHOUN, M.D.
ARCHIVES OF INTERNAL MEDICINE, JANUARY, 1919.

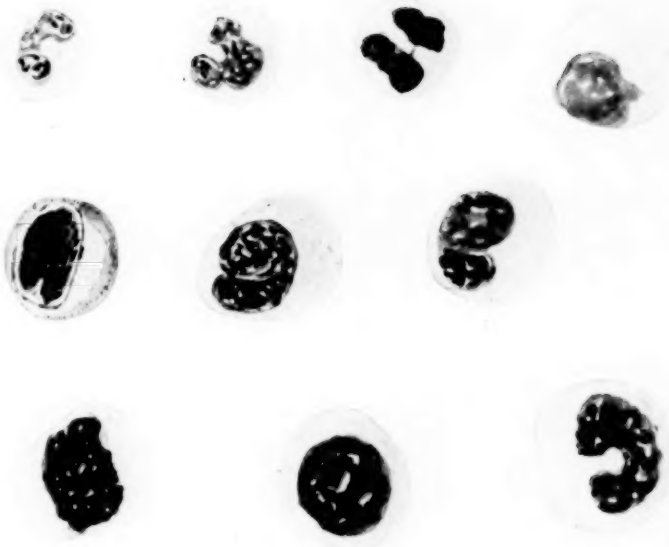

PLATE II

ATYPICAL LARGE LYMPHOCYTES—NONGRANULAR FORM

ILLUSTRATING ARTICLE BY DAVID MURRAY COWIE, M.D., AND HENRIETTA CALHOUN, M.D.
ARCHIVES OF INTERNAL MEDICINE, JANUARY, 1919.

The significance of these cells has never been explained. Schleip remarks that they "are noted in every specimen" and have "no pathologic significance as yet." Their increase in numbers following the injection of typhoid protein would seem to indicate that they really are of pathologic significance.

The nature of the granules is not known. Being acidophil in reaction, their staining is akin to the particles found in eosinophilous cells and to erythrocytes, which are acidophil cells. These granules were also but seldom found in atypical large lymphocyte forms (last line, Fig. 12). Pepper and Miller[11] observed in one animal at the height of the leukocytosis following intravenous typhoid vaccine injection, "phagocytoses of erythrocytes" in smears from the peripheral blood. These phagocytic cells were large mononuclear cells. The same observation has been made in the blood of typhoid patients. So far as we know, the small lymphocyte has no phagocytic power either under normal or abnormal conditions. It seems improbable that these granules can be phagocyted erythrocytes. They stain more brilliantly than do the erythrocytes around them. It seems to us that the red granule is due to some degenerative process or is present in response to some toxic substance.

The reticulated forms were found in the large and small lymphocyte groups. Not many were encountered. The reticulation was either basophil, acidophil or neutrophil. Examples of these cells are shown on lines three, six and seven, Figure 12.

The irregular small lymphocytes consisted of cells with rosette, cross-shaped, mitotic and bizarre formed nuclei. They were present in four out of seven controls and were distinctly more numerous after the intravenous injection. Small atypical forms were almost invariably the predominating cells where high atypical counts were shown.

When atypical large lymphocytes were found the percentage of typical large lymphocytes was always low, but there was no decrease from the preceding counts. The atypical large lymphocytes were almost always forms with a large pale nucleus taking a pale nuclear stain with the chromatin network well preserved. We have taken the ground that the transitional cell belongs in the small lymphocyte group and we do not care to enter any controversy over the possible relationship of the transitionals to these atypical cells. There is still no unaminity of opinion on the transitional question. Without exception, in the ten cases studied there was always an increase over the control in the number of the atypical large cells. We have regarded these as newly formed cells.

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11. Pepper and Miller: J. Infect. Dis., **19**: 1916.

DISCUSSION

The changes in the blood following the injection of a foreign protein (typhoid vaccine) are most remarkable. There is a sudden disappearance of the polymorphonuclear cells, which are soon replaced by an increase amounting in most cases to a hyperleukocytosis. Whether the disappearance is due to a destruction of cells or simply to their deposition in the tissues is not quite clear. The fact that we did not find an increase in the ordinary degenerating cells during the stage of leukopenia inclines us to the opinion that the leukopenia is due to migration. Then again, we are examining only peripheral blood and we have no knowledge of what has happened in the internal circulation. Pepper and Miller think that at least some of the leukocytes are destroyed. They could not find the usual accumulation of leukocytes in smears or tissue sections during the leukopenia stage.

When one watches from hour to hour the procession of cells into the blood stream during the stage of leukocytosis one is impressed with the newness of everything and with the idea that the whole affair is one of genesis. The polynuclears are young and the presence of myelocytes and of nucleated reds points to renewed activity of the respective mesenchymal tissues. Arneth counts made by Pepper and Miller during the leukocytosis showed a great increase in young forms.

The foreign protein seems to have stimulated all the mesenchymal tissues simultaneously. The order in which they are usually called on in infectious processes is, first, the neutrophil leukocytes without immature forms, second, metamyelocytes, third, myelocytes, fourth, promyelocytes, and fifth, megaloblasts (Photakes[12]).

The return of the leukocytes to normal, we believe, indicates that the increased production has ceased and that the excess of cells in the circulation is probably still passing into the tissues.

From these observations it will be seen that no matter what the pathologic condition is, injection of typhoid protein brings forth a similar reaction in all cases. The response differs only in degree. An important observation is that made from Case 3. We had no patient who reacted more violently in a pyrogenic way than this one; during the chill his bed would shake; his sweating was drenching and his pain was acute. He received ten injections, but never gave a leukocyte count above normal. This was a case of long standing. The leukocyte response grew less as the injections increased in number. On the other hand, a similar case, in a child (Case 1) of equally long standing reacted vigorously both pyrogenically and leukocytically. The result in this case was decidedly more marked and the patient still shows improvement two months after the treatment.

12. Photakes: Deutsch. med. Wchnschr., Oct. 28, 1915.

The cases which showed the most improvement are 5, 8, 9, 10 and 1, all of which responded with marked leukocytosis, atypical cells and abnormal cells. All showed a marked myelocyte production and nucleated reds.

Cases 2 and 3 showed only slight myelocytic reaction. In the reactions (1, 2, 4) where myelocytes occurred in Case 3, the patient was very much better following the reactions. In the latter reactions no myelocytes were found, and he made very little if any improvement.

While nucleated red cells are present in most of the reactions where improvement was marked, they were also present in other cases.

An interesting observation is made in Case 4. This patient reacted with marked pyrogenic and leukocytic changes. The simplicity of the blood counts is remarkable. She showed no transitionals, no eosinophils, and in only one count were normal large lymphocytes present. Megalocytes occurred once in each of the two reactions studied; very few. No nucleated red cells were found. Atypical cells, though high at times, did not go far above the number in the control. These were almost entirely of the small lymphocyte type, atypical large cells being present in only three counts. These findings are of importance because of their association with a developmental absence of the epiphyses.

A CONSIDERATION OF THE ANALOGY BETWEEN THE TYPHOID PROTEIN PAROXYSM AND THE MALARIAL PAROXYSM

When we place side by side a series of temperature charts of typhoid protein reactions with the interval temperature curves between we have a very good picture of a case of simple tertian malaria. When we consider the mechanism at work producing the febrile reaction in each case we are still more impressed with their similarity. It is classic knowledge that the malarial paroxysm is associated with the birth of a new crop of young parasites, or due to it. We think there is every reason to warrant us in believing that the malarial paroxysm is a protein reaction due to the death of the parent cell, setting free in the blood stream a dose of dead malarial protein, and this brings about a group of symptoms analogous to or almost identical with that induced by the intravenous injection of typhoid protein.

In the reactions we have watched we note early slightly unpleasant feelings preceding slight chilliness, which frequently develops into a definite chill with rigor; then there is marked elevation of temperature, a general feeling by the patient of heat and a localized increase in the affected parts. This in turn is frequently followed by profuse sweating. The protein paroxysm lasts from eight to fifteen hours, when the patient again feels as well as before the reaction.

We are unable to find any record of consecutive or successive differential counts during a malarial paroxysm. At one time the absence of leukocytosis, with a rapidly rising temperature was con-

sidered "corroborative of malaria." A relative leukocytosis has been observed with a diminishing of the leukocytes toward the end of the reaction.

Krause[7] reports a large number of differential counts on malaria patients. These counts were made at various times during a paroxysm on different patients, but no consecutive counts were made. He found a relative increase in the lymphocytes and a decrease in the polymorphonuclears, excepting from the beginning of the paroxysm up to about the fastigium or later, when there may be a decided absolute and relative increase in the polynuclears. He also noted at times a marked polymorphonuclear leukocytosis without the high fever; especially was this the case in an old infection. These findings fit in quite well with our findings during a protein paroxysm. It would be of great value to have a series of hourly counts during a malarial paroxysm.

The etiologic analogy between the two conditions is quite marked in the typhoid protein paroxysm. There is a billion dose of dead typhoid bacilli set free in the blood stream. It has been shown that in order to infect a mosquito the patient's blood must contain one crescent to every 500 leukocytes. It has also been shown that there may be from sixty-seven to ninety-two crescents per hundred leukocytes. A simple calculation will show that if this is the case, an ounce of blood might easily contain one billion malarial parasites; when these die the analogy is complete, a billion dose of dead malarial parasites has been set free in the blood stream and the typical reaction follows.

CONCLUSIONS

1. No matter what the condition is an intravenous injection of typhoid protein (vaccine) almost invariably initiates a leukopenia followed by a leukocytosis which is associated with, but not necessarily proportional to, the pyrogenic reaction.

2. The induced leukocytosis is chiefly polymorphonuclear even in those cases in which there is an initial lymphocyte increase.

3. A marked feature of the protein reaction is the appearance of atypical cell forms, particularly in the lymphocyte group; accompanying these there are nucleated reds and myelocytes.

4. We are inclined to the opinion that during the leukopenia stage the polynuclears leave the blood stream and enter the tissues, and that the subsequent increase in cells is due to an overproduction of cells from the respective mesenchymal fundaments, as is witnessed by the presence of myelocytes and nucleated reds. This view is further substantiated by the clinical findings of increased joint heat and swelling.

5. The temperature reaction and the clinical findings are not in the nature of an anaphylactic response, as is shown by the absence of an eosinophilia.

6. The cyanosis observed is not due to methemoglobin.

7. Improvement is most marked following those reactions in which there is a good myelocytic response. This is probably a measure of the capacity of the body to react.

8. The marked similarity between the typhoid protein paroxysm and the malarial paroxysm leads us to the belief that their production is due to a common etiologic factor — dead protein. The death of the malarial parasite sets free in the blood stream a sufficient amount of malarial protein to produce the typical protein reaction. The malarial paroxysm, therefore, is not due to the presence of the new organisms, as has been suggested, but to the death of the old ones.

We wish to acknowledge the kind assistance of Drs. Walthall, Beavin, and Kempton, members of the Pediatric Staff, in making leukocyte counts and clinical records.

The tables accompanying the article of Drs. Cowie and Calhoun will be found on the next and following pages.

TABLE 1.—Case 1. Florence S., Aged 11½ Years.—

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells
11/16/17 2:00 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	54	0	0	31	13	2	0
Number	7,200	3,888	0	0	1,332	936	144	0
11/19/17 First injection. Dose 500,000,000 T. V.								
12:15 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	.....	.....	....	.....	.....	.....	....
Number	.....	.....	.....	....	.....	.....	.....	....
1:15 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	77½	0	0	20	2	½	0
Number	5,400	4,175	0	0	1,080	108	27	0
2:15 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	75	1	0	20	2	0	0
Number	5,000	3,750	50	0	1,100	100	0	0
4:15 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	88½	3½	0	4	3	½	0
Number	11,400	9,089	398	0	456	342	57	0
11/22/17 Second injection. Dose 1,000,000,000 T. V.								
1:30 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	56	3	0	21½	16	3	0
Number	4,900	2,745	147	0	1,051	785	147	0
2:30 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	.....	.....	....	.....	.....	.....	....
Number	.....	.....	.....	....	.....	.....	.....	....
3:30 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	61	1	0	29	6	1	0
Number	2,300	1,403	23	0	667	138	23	0
4:30 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	88½	0	0	7	2½	.	0
Number	5,200	4,602	0	0	364	130	52	0
5:45 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	80	1½	0	3	3½	½	0
Number	5,200	4,628	78	0	156	192	26	0
6:45 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	89½	1	0	4	4	1	0
Number	5,600	4,812	56	0	224	224	56	0
8:00 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	86	0	0	5	4	4	0
Number	14,300	13,470	0	0	725	580	580	0
9:00 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	91	0	½	5	2	0	0
Number	15,900	14,469	0	80	795	318	0	0

Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Spectroscopic	Clinical
.....	.....	0						
0	0							
0	0							
.....	.....	...	....	98.4	84	..	Oxy. Hb.	Injected at 12:15
.....	.....							
.....	.....							
.....	.....	1	....	100.4	..	..	Oxy. Hb.	1:05 p. m. chill
0	0							
0	0							
.....	.....	4	....	102.2	84	..	Oxy. Hb.	Nauseated
0	2							
0	100							
.....	.....	0	....	102.4	90	19	Oxy. Hb.	Freer movement
0	½							
0	57							
.....	.....	0	....	99.0	78	20	Oxy. Hb.	Injected at 1:30 p. m.
0	½							
0	25							
.....	.....	...	....	102.4	80	20	Oxy. Hb.	2:00 p. m. chill lasting 45 minutes
.....	.....							
.....	.....							
.....	.....	2		103.0	86	23	Oxy. Hb.	
0	2							
0	46							
.....	.....	0	....	104.8	82	22	Oxy. Hb.	Nauseated; pain in back
½	½							
B 26	26							
.....	.....	0	....	103.0	98	32	Oxy. Hb.	
0	1							
0	52							
.....	.....	0	....	102.0	88	24	Oxy. Hb.	
0	½							
0	28							
.....	.....	0	....	102.2	98	36	Oxy. Hb.	Pain in back
0	3							
0	485							
.....	.....	0	....	102.2	88	22		
0	½							
0	79							

TABLE 1.—Case 1. Florence S., Aged 11½ Years.—

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells
11/23/17 7:00 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	88½	1	0	6	3½	1	0
Number	12,800	10,328	128	0	768	448	128	0
11/25/17 Third injection. Dose 1,000,000,000 T. V. 9:30 a. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	.....	.....	....	.....	.....	.....	....
Number	.....	.....	.....	....	.....	.....	.....	....
10:30 a. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	47	0	0	37	20	4	0
Number	2,000	940	0	0	740	400	80	0
12 noon	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	73	4	0	10	6	1	0
Number	4,000	2,920	160	0	400	240	40	0
1:00 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	83	3	0	3	4	1	1
Number	5,100	4,233	153	0	153	204	51	51
2:00 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	83½	3	½	5	6	1	0
Number	5,200	4,342	156	26	260	312	52	0
3:00 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	84	3	0	5	5	2	0
Number	5,600	4,707	168	0	280	280	112	0
4:30 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	93	½	0	5	½	0	0
Number	27,600	25,688	138	0	1,380	138	0	0
6:00 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	80	2	0	12	3	1	½
Number	19,500	15,600	390	0	2,340	585	195	98
7:30 p. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	91	½	0	5½	2	½	0
Number	16,000	14,560	80	0	640	320	80	0
11/26/17 11:00 a. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	55½	1½	0	26	9½	3	0
Number	10,800	9,990	1,620	0	2,808	1,026	324	0
11/29/17 9:00 a. m.	.....	.....	.....	....	.....	.....	.....	....
Per cent.	100	68	5		15½	6½	2	1
Number	6,100	4,148	305		945	397	122	61

—Chronic Polyperiarthritis Deformans—(*Continued*)

Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Spectroscopic	Clinical
.....	.....	0	....	98.4	76	20		
0	0							
0	0							
.....	.....	...	....	9:40 a. m. 99.2	..	..	.....	Injected at 9:20 a. m.; 9:40 chill
.....	.....							
.....	.....							
.....	.....	0	....	100.0	80	26	Oxy. Hb.	
2	0							
40	0							
.....	.....	0	....	102.0	86	32	Oxy. Hb.	Pain in back
0	6							
0	240							
.....	.....	0	....	101.6	100	38	Oxy. Hb.	
3	2							
B 153	102							
.....	.....	0	....	101.0	82	32	Oxy. Hb.	
1½	½							
B 78	26							
.....	.....	0	....	100.8	80	29	Oxy. Hb.	
1	0							
B 56	0							
.....	.....	0	....	100.0	78	26	Oxy. Hb.	
0	1							
0	276							
.....	.....	0	....	99.6	80	26	Oxy. Hb.	
½	1							
B 97	196							
.....	.....	0	....					
0	½							
0	80							
.....	.....	0	....	....	..	..	Oxy. Hb.	
2	2½							
B 218	470							
.....	.....	0	....					
0	2							
0	122							

TABLE 2.—CASE 2. MRS. W., AGED 59. CHRONIC PERIARTHRITIS; NO STRUCTURAL CHANGE

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
4/19/18																
Tenth injection.																
Dose 1,000,000,000 T. V.																
8:45 a. m.	.....	.....	.....	.....	.....	.....	...	...	.....	.....	0	...	97.6	90	20	Injected at 9 a. m.
Per cent.	100	65	0	0	37½	0	0	0	0	3½						
Number	10,900	7,085	0	0	4,098	0	0	0	0	381						
9:30 a. m.	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0					
Per cent.	100	63½	½	1½	30	0	½	0	0	4						
Number	5,600	4,056	28	84	1,080	0	28	0	0	224						
10 a. m.	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0	...	97.6	90	20	Severe chill
Per cent.	100	59½	0	½	36	½	½	0	0	3						
Number	4,200	2,499	0	21	1,512	21	21	0	0	126						
10:30 a. m.	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0	...	....	...	...	Headache, nausea
Per cent.	100	85	0	1	12½	0	0	0	0	1½						
Number	11,000	9,350	0	110	1,375	0	0	0	0	165						
11 a. m.	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0	...	101.5	108	24	
Per cent.	100	85	0	2	10	0	0	0	0	3						
Number	9,400	7,809	0	188	940	0	0	0	0	282						
12 noon	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0	...	101.6	108	28	
Per cent.	100	88	0	0	12	0	0	0	0	0						
Number	11,300	9,944	0	0	1,356	0	0	0	0	0						
1 p. m.	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0					
Per cent.	100	82½	1	0	12½	0	0	0	½	3½						
Number	10,400	8,580	104	0	1,300	0	0	0	B 52	364						
2 p. m.	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0	...	100.4	96	24	
Per cent.	100	66	0	0	19½	1	½	0	0	4						
Number	11,700	7,722	0	0	2,282	117	58	0	0	468						
3 p. m.	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0	...	100.4	90	24	
Per cent.	100	81½	0	0	16	½	0	0	0	2						
Number	12,500	10,188	0	0	2,000	62	0	0	0	250						
4 p. m.	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0	...	99.0	90	24	
Per cent.	100	76½	1	0	22½	0	0	0	0	0						
Number	16,500	12,929	169	0	3,802	0	0	0	0	0						
5 p. m.	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0					
Per cent.	100	83	½	0	9½	1	½	0	0	5½						
Number	14,000	12,118	73	0	1,387	146	73	0	0	803						
6 p. m.	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0	...	99.2	90	24	
Per cent.	100	82½	0	0	17½	0	0	0	0	0						
Number	14,500	11,963	0	0	2,537	0	0	0	0	0						
7 p. m.	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0	...	99.1	84	20	
Per cent.	100	83	0	0	16½	0	0	0	0	½						
Number	12,000	9,960	0	0	1,980	0	0	0	0	60						
8 p. m.	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0	...	99.0	88	20	
Per cent.	100	74	0	½	18½	5½	0	0	0	½						
Number	11,700	8,658	0	58	2,165	643	0	0	0	176						
9 p. m.	.....	.....	.....	.....	.....	.....	.....	...	.....	.....	0					
Per cent.	100	74½	0	½	24	0	½	0	0	½						
Number	11,000	8,195	0	55	2,640	0	55	0	0	55						

Per cent.	100	74½	0	½	24	0	½	0	0	½						
Number	11,000	8,195	0	55	2,640	0	55	0	0	55						

TABLE 3.—Case 3. Blais., Aged 59. Chronic Infectious Polyperiarthritis Deformans

Date and Hour	Total Leukocysts	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
1/28/18																
12:30 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	59½	0	½	32	½	0	0	½	7						
Number	9,000	4,860	0	45	2,880	45	0	0	E 45	630						
5 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	60	½	1	24	½	0	0	0	14						
Number	8,100	4,860	40	81	1,944	41	0	0	0	1,134						
1/29/18																
10 a. m.	....	.....	....	....	.....	.....	....	...	.....	.....	...	...	102.8	90	23	
Per cent.	100															
Number	9,100															
1/30/18																
First injection. Dose 1,000,000,000 T. V.																
10:30 a. m.	....	.....	....	....	.....	.....	....	...	.....	.....	...	...	99.6			Injected at 10:30 a. m.
Per cent.	100															
11 a. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.0			
Per cent.	100	71½	0	½	17	0	0	0	1	10						
Number	5,900	4,219	0	28	1,003	0	0	0	B 59	590						
11:30 a. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.5	...	...	Chill lasting 25 minutes
Per cent.	100	74	0	0	23	½	0	0	0	2½						
Number	5,700	4,218	0	0	1,311	28	0	0	0	143						
12 noon	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.0			
Per cent.	100	79½	0	0	17½	0	0	0	0	3						
Number	7,300	5,704	0	0	1,377	0	0	0	0	219						
1 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.5			
Per cent.	100	82½	0	0	15	0	½	0	½	1½						
Number	9,400	7,745	0	0	1,410	0	47	0	B 47	141						
2 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.3			
Per cent.	100	87	0	½	9	1	0	0	1	1½						
Number	9,000	7,830	0	45	810	90	0	0	B 90	135						
3 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.5			
Per cent.	100	83	0	0	14½	½	0	0	½	1½						
Number	8,100	6,723	0	0	1,174	41	0	0	B 40	122						

TABLE 3.—Case 3. Blais., Aged 59. Chronic Infectious Polyperiarthritis Deformans—(*Continued*)

Date and Hour	Total Leukocysts	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
4 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.7			
Per cent.	100	90	0	0	9	1	0	0	0	0						
Number	8,500	7,650	0	0	765	85	0	0	0	0						
5 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.5			
Per cent.	100	88	0	0	9	1	0	0	0	2						
Number	7,100	6,248	0	0	639	71	0	0	0	142						
6 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.4			
Per cent.	100	79	0	0	17	½	0	0	0	3½						
Number	8,700	6,873	0	0	1,479	44	0	0	0	304						
8:30 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.8			
Per cent.	100	88	0	0	10½	0	0	0	0	1½						
Number	7,400	6,512	0	0	777	0	0	0	0	121						
2/1/18 Second injection Dose 1,000,000,000 T. V.																
10 a. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.4	85	20	Injected at 10:30 a. m.
Per cent.	100	66	0	1	26	4	1	0	0	2						
Number	4,700	3,102	0	47	1,212	188	47	0	0	94						
11 a. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.4	110	24	Chill lasting 25 minutes
Per cent.	100	59½	½	0	33½	½	0	0	0	6						
Number	4,000	2,380	20	0	1,340	20	0	0	0	240						
12 noon	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.6	120	28	
Per cent.	100	67	½	0	30½	½	0	0	0	1½						
Number	8,400	5,628	42	0	2,562	42	0	0	0	126						
1 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.9	120	28	
Per cent.	100	92½	0	0	7	0	0	0	0	½						
Number	8,000	7,400	0	0	560	0	0	0	0	40						
2 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.0	120	32	
Per cent.	100	81½	0	0	17	1	0	0	0	½						
Number	5,700	4,646	0	0	969	57	0	0	0	28						
3 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.8	120	28	
Per cent.	100	92	0	0	6	0	0	0	0	2						
Number	5,700	5,244	0	0	342	0	0	0	0	114						

4 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.0	122	28	
Per cent.	100	89½	0	1½	8	0	0	0	0	1						
Number	6,300	5,639	0	94	504	0	0	0	0	63						
5 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	2					
Per cent.	100	88½	½	0	3	5	2	0	½	½						
Number	7,200	6,372	36	0	216	360	144	0	E 36	36						
7:30 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	2	...	102.2	122	28	
Per cent.	100	89½	0	0	5	3½	½	0	0	1½						
Number	5,900	5,281	0	0	295	206	29	0	0	89						
2/4/18																
Third injection																
Dose 1,000,000,000																
T. V.																
1 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.0	86	22	Injected at 1 p. m.
Per cent.	100	50½	0	0	41	0	0	0	0	8½						
Number	5,000	2,525	0	0	2,050	0	0	0	0	425						
2 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.8	84	22	Chill lasting 20 minutes
Per cent.	100	55	0	0	39½	1½	0	0	0	4						
Number	3,500	1,925	0	0	1,383	52	0	0	0	140						
3 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.0	100	23	
Per cent.	100	88	0	0	16	0	0	0	0	1½						
Number	2,000	1,760	0	0	320	0	0	0	0	30						
4 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.0	120	24	Complains of being very hot
Per cent.	100	84	0	½	12½	0	0	0	0	3						
Number	3,400	2,856	0	17	425	0	0	0	0	102						
6 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.6	112	24	Complains of being very hot
Per cent.	100	87	0	0	10½	½	0	0	0	2						
Number	6,800	5,935	0	0	714	34	0	0	0	136						
7 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.2	102	24	Complains of being very hot
Per cent.	100	85	0	0	12	0	0	0	0	3						
Number	6,400	4,690	0	0	768	0	0	0	0	192						
8 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.2	115	24	
Per cent.	100	79	½	0	15	½	0	0	0	5						
Number	4,300	3,397	22	0	645	21	0	0	0	215						
2/7/18																
7:30 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	...	...	....	...	...	Fourth injection, no counts made
Per cent.	100															
Number	6,900															

TABLE 3.—Case 3. Blais., Aged 59. Chronic Infectious Polyperiarthritis Deformans—(*Continued*)

Date and Hour	Total Leukocysts	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
2/10/18 Fifth injection Dose 1,000,000,000 T. V.																
11 a. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.6	90	20	Injected at 10:30 a. m.
Per cent.	100	58½	0	0	34	½	0	0	½	6½						
Number	6,700	3,920	0	0	2,278	33	0	0	33	436						
12 noon	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.0	92	22	Chill lasting 25 minutes
Per cent.	100	62	0	½	28½	1	½	0	0	7½						
Number	4,500	2,790	0	22	1,283	45	22	0	0	338						
1 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.0	100	22	
Per cent.	100	85	0	0	15	0	0	0	0	0						
Number	5,800	4,930	0	0	870	0	0	0	0	0						
3 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.0	112	22	
Per cent.	100	88½	0	0	11½	0	0	0	0	0						
Number	6,900	6,107	0	0	793	0	0	0	0	0						
5 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.0	120	22	
Per cent.	100	87	0	0	10½	½	0	0	0	2						
Number	7,700	6,699	0	0	809	38	0	0	0	154						
7:30 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.0	114	22	
Per cent.	100	91½	0	0	7½	0	0	0	0	1						
Number	6,800	6,222	0	0	510	0	0	0	0	68						
2/13/18 Sixth injection Dose 1,000,000,000 T. V.																
10:30 a. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.2	100	22	Injected at 10:30 a. m.
Per cent.	100	70	0	0	29	0	0	0	0	1						
Number	6,600	4,620	0	0	1,914	0	0	0	0	66						
12:30 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.2	98	20	
Per cent.	100	70	0	1½	25	½	½	0	0	2½						
Number	4,100	2,870	0	61	1,025	20	21	0	0	103						

1 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	..)	100.5	100	22	
Per cent.	100	83	1	0	15½	⅛	0	0	0	0						
Number	6,700	5,561	67	0	1,099	33	0	0	0	0						
2:30 p. m.	....	.....	....	....	.....	.....	....	..	.....	.....	0	...	103.2	126	23	
Per cent.	100	92	0	0	8	0	0	0	0	0						
Number	9,400	8,684	0	0	752	0	0	0	0	0						
4:30 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.2	120	23	
Per cent.	100	90	0	0	8½	½	0	0	0	1						
Number	6,900	6,210	0	0	587	34	0	0	0	69						
2/17/18 Seventh injection Dose 1,000,000,000 T. V.																
8:30 a. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.0	95	22	Injected at 8:30 a. m.
Per cent.	100	67½	0	½	24	1	½	0	0	6½						
Number	6,600	4,455	0	33	1,584	66	33	0	0	429						
10 a. m.	....	.....	....	....	.....	.....	....	...	.....	.....	1	...	99.0	100	22	
Per cent.	100	72	0	0	21½	4	½	0	0	2						
Number	6,700	4,824	0	0	1,441	268	33	0	0	134						
10:30 a. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.0	115	22	
Per cent.	100	67	0	0	27	2½	1	0	0	2½						
Number	4,200	2,814	0	0	1,134	105	42	0	0	105						
12 noon	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.0	115	22	
Per cent.	100	81½	0	0	15	1	1	0	0	1½						
Number	6,500	5,298	0	0	975	65	65	0	0	97						
1 p. m.	....	.....	....	....	.....	.....	...	...	.....	.....	1	...	102.0	102	22	
Per cent.	100	82	0	0	13½	2	1	0	0	1½						
Number	7,300	5,986	0	0	986	146	73	0	0	109						
3 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.8	102	22	
Per cent.	100	84	0	0	12	1	0	0	0	3						
Number	7,000	5,880	0	0	840	70	0	0	0	210						
5 p. m.	....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.8	102	22	
Per cent.	100	81	0	0	17	0	0	0	0	2						
Number	6,200	5,022	0	0	1,054	0	0	0	0	124						

TABLE 4.—Case 4. Shag., Aged 12. Multiple Periarthritis Deformans and Chronic Arthritis

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
2/24/18 First injection Dose 1,000,000,000 T. V.																
10 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.2	120	25	Injected at 10 a. m.
Per cent.	100	82	0	0	15½	0	0	0	0	2½						
Number	14,700	12,054	0	0	2,279	0	0	0	0	367						
11 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.8	124	25	
Per cent.	100	80	0	½	19	0	0	0	½	0						
Number	5,400	4,320	0	27	1,026	0	0	0	B 27	0						
12 noon	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.0	152	28	
Per cent.	100	91	0	0	9	0	0	0	0	0						
Number	8,100	7,371	0	0	729	0	0	0	0	0						
2 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.2	118	24	
Per cent.	100	94	0	0	6	0	0	0	0	0						
Number	30,900	29,046	0	0	1,854	0	0	0	0	0						
4 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.0	118	26	
Per cent.	100	95	0	0	3	0	0	0	0	2						
Number	22,300	21,185	0	0	669	0	0	0	0	446						
5 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.2	118	27	
Per cent.	100	94½	0	0	5	0	0	0	0	½						
Number	24,800	23,436	0	0	1,240	0	0	0	0	124						
6 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.3	120	26	
Per cent.	100	93	0	0	7	0	0	0	0	0						
Number	26,700	22,831	0	0	1,869	0	0	0	0	0						
4/9/18																
Per cent.	100															
Number	8,900															
4/10/18 Tenth injection Dose 1,000,000,000 T. V.																
8 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.6	...	...	Injected at 8:15 a. m.
Per cent.	100	70½	0	0	22½	1	0	0	0	6						
Number	8,500	5,993	0	0	1,812	85	0	0	0	510						
8:45 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.6			
Per cent.	100	42	0	½	53	0	0	0	0	4½						
Number	2,700	1,134	0	13	1,431	0	0	0	0	122						
9:15 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.4			
Per cent.	100	54½	0	0	44	0	0	0	½	1						
Number	2,800	1,526	0	0	1,232	0	0	0	B 14	28						
9:45 a. m.	.....	.....	....	....	.....	.....	....	..	.....	.....	0	..	102.6	...	...	Chill severe
Per cent.	100	82	0	0	18	0	0	0	0	0						
Number	5,600	4,592	0	0	1,008	0	0	0	0	0						

10:15 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.0		
Per cent.	100	71	0	0	28	0	0	0	0	1					
Number	5,500	3,905	0	0	1,540	0	0	0	0	55					
11:15 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.8		
Per cent.	100	95	0	0	5	0	0	0	0	0					
Number	8,200	7,790	0	0	410	0	0	0	0	0					
12:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.0		
Per cent.	100	98½	0	0	1½	0	0	0	0	0					
Number	10,400	10,244	0	0	156	0	0	0	0	0					
1:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.2		
Per cent.	100	97	0	0	3	0	0	0	0	0					
Number	12,300	11,931	0	0	369	0	0	0	0	0					
2:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0				
Per cent.	100	95	0	0	3	1	0	0	0	1					
Number	14,600	13,870	0	0	438	146	0	0	0	146					
3:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.0		
Per cent.	100	96½	0	0	2½	½	0	0	0	½					
Number	19,600	18,914	0	0	490	98	0	0	0	98					
4:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0				
Per cent.	100	94½	0	0	5	0	0	0	0	½					
Number	22,100	20,885	0	0	1,105	0	0	0	0	110					
5:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.0		
Per cent.	100	93	0	0	7	0	0	0	0	0					
Number	23,800	22,134	0	0	1,676	0	0	0	0	0					
6:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0				
Per cent.	100	91½	0	0	6½	0	0	0	0	2					
Number	20,200	18,483	0	0	1,313	0	0	0	0	404					
7:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.8		
Per cent.	100	88	0	0	12	0	0	0	0	0					
Number	17,800	15,664	0	0	2,136	0	0	0	0	0					
8:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0				
Per cent.	100	75½	0	0	12½	0	0	0	0	3					
Number	13,200	9,966	0	0	2,838	0	0	0	0	396					
9:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.0		
Per cent.	100	75½	0	1	22½	0	0	0	0	1					
Number	9,300	7,022	0	93	2,029	0	0	0	0	93					
10:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.6		
Per cent.	100	75	0	0	25	0	0	0	0	0					
Number	10,400	7,800	0	0	2,600	0	0	0	0	0					
4/11/18															
1 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.0		
Per cent.	100	68½	0	½	27	½	0	0	0	3½					
Number	8,100	5,549	0	40	2,187	40	0	0	0	284					
4/11/18															
7 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	..	99.2		
Per cent.	100	61	0	0	39	0	0	0	0	0					
Number	8,800	5,368	0	0	3,432	0	0	0	0	0					

TABLE 5.—Case 5. Miss W., Aged 22. Acute Rheumatism, Joint Swelling—No Structural Change

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
12/28/17 Control counts																
11 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	62	½	0	29	5	3½	0	0	0						
Number	20,000	12,400	100	0	5,800	1,000	700	0	0	0						
12 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	60	½	½	34	2½	2	0	0	½						
Number	18,800	11,280	94	94	6,392	470	376	0	0	94						
1 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	70½	0	0	23½	4½	1½	0	0	0						
Number	22,100	15,581	0	0	5,194	994	331	0	0	0						
2 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	67	0	½	27	3½	1½	0	0	½						
Number	15,800	10,586	0	79	4,266	553	237	0	0	79						
3 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	69½	½	½	22	2	2	0	½	3						
Number	22,800	15,846	114	114	5,016	456	456	0	N 114	648						
4 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	66	½	0	28	2½	0	½	1½	2						
Number	17,600	11,616	88	0	4,928	440	0	88	N 264	352						
5 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	74	0	0	22	2	1	½	0	1½						
Number	17,300	12,802	0	0	3,406	346	173	87	0	259						
6 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	70½	0	0	26	0	½	0	0	3						
Number	18,100	11,760	0	0	4,706	0	91	0	0	543						
12/29/17 First injection Dose 1,000,000,000 T. V.																
8 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.0	80	20	Injected at 8 a. m.
Per cent.	100	68½	0	9	28½	1	1½	0	0	½						
Number	21,600	14,796	0	0	6,156	216	324	0	0	108						

8:30 a. m.	.....	.....	....	.....	.....	.....	....	...	.....	.....	0	...	99.4	84	20	
Per cent.	100	68	0	½	28½	½	2	0	0	½						
Number	13,300	9,044	0	67	3,791	66	266	0	0	66						
9 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.0	96	20	
Per cent.	100	30	0	1	70	1	1	0	0	0						
Number	6,900	1,970	0	69	4,830	69	69	0	0	0						
9:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	1	...	101.0	92	20	
Per cent.	100	47	0	0	56	1	0	0	0	1						
Number	6,500	3,055	0	0	3,640	65	0	0	0	65						
10 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.6	104	22	
Per cent.	100	68	0	0	30	1	½	0	0	½						
Number	8,000	5,440	0	0	2,400	80	40	0	0	40						
10:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.5	120	20	
Per cent.	100	74	0	0	22	0	2	0	0	2						
Number	9,500	7,030	0	0	2,090	0	190	0	0	190						
11 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.6	108	20	
Per cent.	100	80	0	0	15	1	4	0	0	0						
Number	12,400	9,920	0	0	1,860	124	496	0	0	0						
11:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	...	...	103.6	108	20	
Per cent.	100															
12 noon	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	...	...	...	Sleeping
Per cent.	100	92½	0	0	7½	0	0	0	0	0						
Number	15,000	13,875	0	0	1,125	0	0	0	0	0						
1 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.4	100	20	
Per cent.	100	88	0	0	5	0	3	0	0	4						
Number	24,500	21,560	0	0	1,225	0	735	0	0	980						
2 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.4	96	20	
Per cent.	100	92	0	0	5½	0	2	0	0	½						
Number	16,000	14,720	0	0	880	0	320	0	0	80						
3 p. m.	.....	.....	....	.....	.....	.....	.....	...	.....	.....	0	...	101.8	102	20	
Per cent.	100	91½	0	½	6	0	½	0	0	1½						
Number	32,000	29,280	0	160	1,920	0	160	0	0	480						
4 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.0	96	20	
Per cent.	100	90	0	0	7	½	0	0	0	2½						
Number	28,600	25,740	0	0	2,002	143	0	0	0	715						
5 p. m.	.....	.....	....	....	.....	.....	½	...	.....	.....	0	...	102.0	108	20	
Per cent.	100	94½	0	0	2½	½	½	0	0	2						
Number	24,900	23,531	0	0	622	124	125	0	0	498						

TABLE 5.—Case 5. Miss W., Aged 22. Acute Rheumatism, Joint Swelling—No Structural Change—(*Continued*)

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso-Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
6 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	104.0	102	20	
Per cent.	100	91½	0	0	7	0	½	0	½	½						
Number	31,400	28,731	0	0	2,198	0	157	0	B 157	157						
7 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	104.0	102	20	
Per cent.	100	90	0	0	8	0	0	0	½	1½						
Number	20,400	18,200	0	0	1,632	0	0	0	B 102	306						
8 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.8	96	20	
Per cent.	100	69	0	0	14	5	5	1	0	6						
Number	18,200	10,158	0	0	2,548	910	910	182	0	1,092						
9 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	104.0	94	20	
Per cent.	100	88½	0	0	5	3	1½	0	1	1						
Number	20,300	17,966	0	0	1,015	609	304	0	B 203	203						
10 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	...	...	105.0	96	20	
Per cent.	100															
1/1/18 Second injection Dose 1,000,000,000 T. V.																
8 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.6	80	20	
Per cent.	100	62½	0	0	31	1½	½	0	½	4						
Number	4,400	2,750	0	0	1,364	66	22	0	B 22	176						
9 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.6	80	20	Injected at 9 a. m.
Per cent.	100	59½	0	0	30	2½	1½	0	0	6½						
Number	4,700	2,797	0	0	1,410	117	71	0	0	305						
9:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.6	120	28	
Per cent.	100	59½	0	0	35½	1	½	0	0	3½						
Number	2,800	1,666	0	0	994	28	14	0	0	98						
10 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.0	120	28	Severe chill lasting 20 minutes
Per cent.	100	25	0	0	65	5	2	0	1	2						
Number	2,500	625	0	0	1,625	125	50	0	B 25	50						
10:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.0	116	28	
Per cent.	100	64	0	0	27	3	4	1	0	1						
Number	2,900	1,856	0	0	783	87	116	29	0	29						

11 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.2	116	24	
Per cent.	100	71	0	1	19	2	0	0	1	6						
Number	2,600	1,846	0	26	494	52	0	0	N 26	216						
12 noon	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.8	88	26	
Per cent.	100	83	0	0	7	4	3	1	0	2						
Number	4,500	3,735	0	0	315	180	135	45	0	90						
1 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.6	100	24	
Per cent.	100	82	0	0	16	1	0	0	0	1						
Number	7,600	6,232	0	0	1,216	76	0	0	0	76						
2 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.3	96	24	
Per cent.	100	92½	0	0	6	1	0	0	0	½						
Number	6,500	6,013	0	0	390	65	0	0	0	37						
3 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.4	96	24	
Per cent.	100	84	0	1	13½	0	0	0	0	1½						
Number	5,300	4,452	0	53	716	0	0	0	0	120						
4 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	...	...	102.6	100	24	
Per cent.	100															
Number	6,000															
5 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.2	96	20	
Per cent.	100	76½	0	0	18	2½	1½	0	0	1½						
Number	6,600	5,049	0	0	1,188	165	99	0	0	99						
6 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.6	108	24	
Per cent.	100	68½	0	0	27	0	½	0	½	3½						
Number	5,300	3,631	0	0	1,431	0	27	0	27	186						
7 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.2	108	22	
Per cent.	100	64	0	0	28½	2	2	0	½	3						
Number	5,900	3,776	0	0	1,681	118	118	0	30	177						
8 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.0	88	20	
Per cent.	100	63½	0	0	32	½	0	0	0	4						
Number	4,300	2,731	0	0	1,376	26	0	0	0	172						
1/18/18 Third injection Dose 1,000,000,000 T. V.																
1 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.8	92	22	Injected at 1 p. m.
Per cent.	100	55	0	½	39½	3	1½	0	0	½						
Number	10,000	5,500	0	50	3,950	300	150	0	0	50						
1:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.8	98	20	
Per cent.	100	41	1	0	56	1	1	0	0	0						
Number	10,300	4,223	103	0	5,768	103	103	0	0	0						

TABLE 5.—Case 5. Miss W., Aged 22. Acute Rheumatism, Joint Swelling—No Structural Change—(*Continued*)

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso-Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
2 p. m.	.....	.....	....	....	.....	.....	.....	...	.....	.....	0	...	98.8	98	20	
Per cent.	100	66	0	0	29	1½	1½	0	0	2						
Number	9,900	6,534	0	0	2,871	1,465	1,465	0	0	198						
2:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.0	100	22	Severe chill lasting from 2:30-3:10
Per cent.	100	59	0	0	34	6	1	0	0	0						
Number	8,500	5,015	0	0	2,890	510	85	0	0	0						
3 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.2	102	22	
Per cent.	100	73½	0	0	26½	0	0	0	0	0						
Number	6,200	4,557	0	0	1,643	0	0	0	0	0						
4:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.2	124	24	Still complains of cold; nauseated
Per cent.	100	76½	0	0	21	1	1	0	0	½						
Number	4,400	3,366	0	0	924	44	44	0	0	22						
5 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.8	124	22	
Per cent.	100	72	0	0	17	3	3	0	0	0						
Number	5,400	3,788	0	0	918	162	162	0	0	0						
6 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.6	120	24	
Per cent.	100	86	0	0	11	2	1	0	0	0						
Number	10,500	9,030	0	0	1,155	210	105	0	0	0						
7 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.4	120	24	
Per cent.	100	92½	0	0	2½	1½	2½	0	½	½						
Number	13,600	12,580	0	0	336	200	336	0	N 68	68						
8 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.8	116	24	
Per cent.	100	91½	0	½	4	1½	2	0	0	½						
Number	20,400	18,666	0	102	816	306	408	0	0	102						
9 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.0	108	24	
Per cent.	100	90	0	0	6½	1½	1½	0	0	½						
Number	11,400	10,360	0	0	641	171	171	0	0	57						
10 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.0	102	22	
Per cent.	100	87	0	0	5½	2½	4	0	½	½						
Number	15,100	13,137	0	0	830	378	604	0	N 76	75						
11 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	...	...	100.8	96	22	
Per cent.	100															
12	.....	.....	....	....	.....	.....	....	...	.....	.....	...	...	100.0	92	22	
Per cent.	100															

TABLE 6.—Case 6. Miss Wor., Aged 22. Hypertrophic Arthritis

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso-Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	perature	Pulse	Respiration	Clinical
12/25/17 Fourth injection Dose 1,000,000,000 T. V.																
9 a. m.	.....	.....	....	....	.....	.....	....	...	.....	...	0	.....	...	...	...	Injected at 9:05 a. m.
Per cent.	100	70½	0	0	21½	3	2	0	0	3						
Number	7,200	5,076	0	0	1,548	216	144	0	0	216						
9:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	...	0					
Per cent.	100	70½	0	0	23	1½	1	0	1	3						
Number	7,200	5,076	0	0	1,656	108	72	0	B 72	216						
10 a. m.	.....	.....	....	....	.....	.....	....	...	.....	...	0	.....	98.6	92	20	
Per cent.	100	65	0	½	25	2½	1½	0	½	5						
Number	8,700	5,655	0	43	2,175	44	131	0	B 43	435						
10:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	...	0	Well preserved and large plates ½–¾ size of the reds	98.2	88	20	
Per cent.	100	64	0	0	33	0	0	0	0	3						
Number	6,500	4,160	0	0	2,145	0	0	0	0	0						
11 a. m.	.....	.....	....	....	.....	.....	....	...	.....	...	0	.....	98.2	88	20	
Per cent.	100	69½	0	0	28	½	0	0	0	2						
Number	6,600	4,587	0	0	1,848	33	0	0	0	132						
12 noon	.....	.....	....	....	.....	.....	....	...	.....	...	0	.....	98.4	92	20	
Per cent.	100	58	0	0	34	1	½	0	1½	5						
Number	7,200	4,176	0	0	2,448	72	36	0	B 108	360						
1 p. m.	.....	.....	....	....	.....	.....	....	...	.....	...	0	.....	98.8	86	20	No nausea, vomiting nor chilly sensation; comfortable thruout the entire period
Per cent.	100	69½	0	0	21½	2½	1½	0	0	5						
Number	9,700	6,741	0	0	2,086	242	146	0	0	485						
2 p. m.	.....	.....	....	....	.....	.....	....	...	.....	...	0	.....	98.8	86	20	
Per cent.	100	52½	0	0	41½	0	1	0	1	4						
Number	8,500	4,463	0	0	3,527	0	85	0	85	340						
3 p. m.	.....	.....	....	....	.....	.....	....	...	.....	...	0	.....	98.4	90	20	
Per cent.	100	68½	0	0	24½	1½	0	0	0	5½						
Number	10,100	6,919	0	0	2,474	1,061	0	0	0	555						
4 p. m.	.....	.....	....	....	.....	.....	....	...	.....	...	0					
Per cent.	100	70½	0	0	27½	0	0	0	0	2						
Number	11,000	7,755	0	0	3,025	0	0	0	0	220						
5 p. m.																
Per cent.	100	65	0	0	28½	3½	1	0	0	2						
Number	9,700	6,305	0	0	2,764	339	97	0	0	194						

TABLE 7.—Case 7. Mrs. McD. Atrophic Arthritis

Blood exam. 12/22/17. Reds 5,180,000. Hb. 80 per cent.

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso-Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Blood Pressure, Syst.	Clinical
11/6/17																
First injection																
Dose 500,000,000																
T. V. intravenous																
12 noon	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.0	72	125	Injected at 12:15
Per cent.	100	56	1	0	37	2	3	1	0	0						
Number	5,200	2,912	52	0	1,942	104	156	52	0	0						
2:45 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	.....	...	114	
Per cent.	100	50	1	0	32	13	4	0	0	0						
Number	6,700	3,350	67	0	2,144	871	268	0	0	0						
3:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	97.8	72	111+	Occipital headache
Per cent.	100	53	4	2	29	10	2	0	0	0						
Number	6,200	3,286	248	124	1,798	620	124	0	0	0						
4:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	97.8	68	112	5:07 p. m. chill
Per cent.	100	49	3	1	34	12	1	0	0	0						
Number	5,200	2,548	156	52	1,768	624	52	0	0	0						
5:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	....	...	97.8	64	114	
Per cent.	100															
Number	11,500															
5:45 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.6	54	114	
Per cent.	100	84	0	1	13	0	2	0	0	0						
Number	10,900	9,156	0	109	1,417	0	218	0	0	0						
6:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	....	...	100.6	80	114	Severe pain in legs and back
Per cent.	100															
Number	9,400															
8:45 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.4	80	114	Frequent urination
Per cent.	100	90	0	0	7	1½	1½	0	0	0						
Number	9,700	8,730	0	0	679	146	145	0	0	0						
11/7/17																
6 p. m.																
Number	6,200															
11/8/17																
Second injection																
Dose 1,000,000,000																
T. V.																
2 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	.....	...	...	Injected at 2 p. m.
Per cent.	100	35	3	2	38	15	7	0	0	0						
Number	8,000	2,800	240	160	3,040	1,200	560	0	0	0						
2:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.6	58	114	
Per cent.	100	51	5	1	24	11	2	0	1	5						
Number	8,200	4,182	410	82	1,968	902	164	0	B. 82	410						

3 p. m.	.....	.....	....	....	.....	.....	....	....	.....	.....	0	...	97.8	60	112	Pain in back and legs
Per cent.	100	57	5½	½	27	5½	2	½	1	1						
Number	5,700	3,249	303	28	1,539	303	114	28	B. 57	57						
4 p. m.	.....	.....	....	....	.....	.....	....	....	.....	.....	0	Very large	98.8	68	111	4:40 p. m. severe chill
Per cent.	100	62	5	0	17½	8	2	0	½	0						
Number	9,000	5,580	450	0	1,575	720	180	0	E. 45	0						
5 p. m.	.....	.....	....	....	.....	.....	....	....	.....	.....	0	...	100.0	84	114	
Per cent.	100	73½	2½	0	18	3½	1½	½	0	½						
Number	10,700	7,856	267	0	1,926	375	160	53	0	54						
6 p. m.																
Per cent.	100															
Number	6,200															
11/12/17																
Third injection																
Dose 1,000,000,000 T. V.																
2:45 p. m.	.....	.....	....	....	.....	.....	....	....	.....	.....	0	...	98.2	68	113	Injected at 1:45 p. m.
Per cent.	100	77	5	0	10½	5	1	0	1½	0						
Number	5,400	4,158	270	0	577	270	54	0	B. 81	0						
3:45 p. m.	.....	.....	....	....	.....	.....	....	....	.....	.....	0	...	98.2	68	112	4:35 p. m. pain in neck
Per cent.	100	56	1	1	28	10	3	0	1	0						
Number	4,300	2,408	43	43	1,204	430	129	0	B. 43	0						
4:45 p. m.	.....	.....	....	....	.....	.....	....	....	.....	.....	0	...	99.2	68	112	Chill of 45 minutes duration
Per cent.	100	63	3	0	20	9	4	1	0	0						
Number	? 900	2,457	117	0	780	351	146	39	0	0						
4:45 p. m.	.....	.....	....	....	.....	.....	....	....	.....	.....	0	...	.....	...	...	Severe pain
Per cent.	100	78	5	0	5	10	2	0	0	0						
Number	4,400	3,432	220	0	220	440	88	0	0	0						
7 p. m.	.....	.....	....	....	.....	.....	....	....	.....	.....	....	...	102.0	92	114	
Per cent.	100															
Number	4,200															
8 p. m.	.....	.....	....	....	.....	.....	....	....	.....	.....	2	Large	102.4	70	113	Occasional dropped beat at wrist
Per cent.	100	84	2	1	5	3	2	0	0	0						
Number	7,800	6,552	156	78	390	273	156	0	0	0						
9:30 p. m.	.....	.....	....	....	.....	.....	....	....	.....	.....	0	Many large	102.2	84		
Per cent.	100	86	2	½	7	1½	1	0	½	1½						
Number	10,900	9,374	218	54	756	164	109	0	B. 54	164						
11/15/17																
1:30 p. m.	.....	.....	....	....	.....	.....	....	....	.....	.....	0					
Per cent.	100	64	4	2	20	9	1	0	0	0						
Number	5,900	3,776	236	118	1,180	531	59	0	0	0						
12/22/17																
3:30 p. m.	.....	.....	....	....	.....	.....	....	....	.....	.....	0					
Per cent.	100	56	1	½	29	8½	2½	1½	1	0						
Number	5,500	3,080	55	27	1,595	468	137	83	B. 55	0						

TABLE 8.—Case 8. Mrs. B., Aged 46. Hypertrophic Arthritis of Spine

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso-Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
2/7/18																
2:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.4	78	20	
Per cent.	100	66	1	0	26½	4	1	½	0	1						
Number	6,100	4,026	61	0	1,617	244	61	30	0	61						
2/8/18																
First injection																
Dose 1,000,000,000																
T. V.																
8:10 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	97.4	78	20	Injected at 8:12 a. m.
Per cent.	100	54	1	0	40	4	1	0	0	0						
Number	6,250	3,375	63	0	2,490	249	62	0	0	0						
8:45 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	97.6	80	18	Chill
Per cent.	100	48	2½	1½	41	4	1	0	0	1						
Number	3,450	1,656	86	52	1,449	138	35	0	0	34						
9:15 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.6	93	21	
Per cent.	100	36	½	0	49½	5½	2½	0	½	5½						
Number	4,700	1,692	24	0	2,326	259	117	0	23	259						
9:45 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.8	110	23	
Per cent.	100	48	1	0	37	5	2	0	1	6						
Number	3,850	1,848	39	0	1,544	172	76	0	39	2,310						
10:15 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	1	...	102.9	115	24	Nausea, cyanosis, spectrosc., Oxy. Hb.
Per cent.	100	63	0	0	25	5	4	0	0	3						
Number	2,000	1,260	0	0	500	100	80	0	0	60						
11:15 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.2	128	24	Pain in legs and back
Per cent.	100	75½	0	0	16	3½	4	0	0	1						
Number	2,750	2,831	0	0	600	131	150	0	0	38						
12:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.3	123	23	Delirious, severe pain
Per cent.	100	79	0	0	7½	5½	5	0	0	3						
Number	9,200	7,168	0	0	689	506	460	0	0	276						
1:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.8	119	23	Severe pain, spectrosc., Oxy. Hb.
Per cent.	100	80	0	0	6	3	4	0	2½	4½						
Number	9,000	7,200	0	0	540	270	360	0	225	405						
2:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	1	...	102.5	119	33	More comfortable
Per cent.	100	89	0	0	7½	½	½	0	1	1½						
Number	12,400	11,036	0	0	930	62	62	0	124	186						
3:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.2	102	26	
Per cent.	100	85	0	0	6	4½	3	0	1	½						
Number	12,100	10,185	0	0	726	544	363	0	B. 121	61						

4:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.8	109	25	
Per cent.	100	92	0	0	2½	3	1	0	0	1½						
Number	8,250	7,590	0	0	206	248	82	0	0	124						
5:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.0	112	27	
Per cent.	100	94½	0	0	3½	½	0	0	0	½						
Number	20,200	19,089	0	0	707	101	0	0	0	101						
6:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.8	110	22	
Per cent.	100	88	½	0	3½	2½	3½	0	½	1½						
Number	15,700	13,816	79	0	549	392	549	0	79	236						
7:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.8	110	22	Headache, restless
Per cent.	100	89	1½	0	1	4	3½	0	0	1						
Number	24,750	22,057	371	0	248	990	866	0	0	248						
8:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.2	80	27	
Per cent.	100	98½	0	0	½	½	0	0	0	½						
Number	23,400	23,049	0	0	117	117	0	0	0	117						
9:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	2	...	101.0	80	30	Morphin sulphate ⅙ gr. [H]
Per cent.	100	89	0	0	2	5½	2	0	1½	0						
Number	28,100	25,009	0	0	562	1,546	562	0	B. 422	0						
10:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	1	...	100.8	80	40	Still is cyanotic
Per cent.	100	86	½	0	7	3½	2	0	0	1						
Number	28,700	24,782	144	0	2,009	1,004	574	0	0	287						
11:05 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	1	...	100.4	100	34	
Per cent.	100	83½	0	0	6½	4½	3	0	1	1½						
Number	28,600	23,881	0	0	1,859	1,287	858	0	B. 286	429						
2/9/18																
11:15 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.2	92	27	
Per cent.	100	81½	½	½	9	1½	1	0	3	3						
Number	23,300	18,991	116	116	2,097	350	233	0	699	699						
5:15 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.1	83	20	
Per cent.	100	80½	½	0	8	3	2	0	1	5						
Number	32,700	26,323	164	0	2,616	981	654	0	B. 327	1,635						
2/11/18																
Second injection																
Dose 500,000,000																
T. V.																
8:10 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.4	78	19	Injected at 8 a. m.
Per cent.	100	55	0	0	41	1	2	0	1	0						
Number	8,600	4,730	0	0	3,526	86	172	0	B. 86	0						
8:40 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.6	81	21	Severe chill lasting 20 minutes
Per cent.	100	50½	0	0	43	2	½	½	½	3						
Number	6,100	3,081	0	0	2,623	122	30	31	B. 30	183						

TABLE 8.—Case 8. Mrs. B., Aged 46. Hypertrophic Arthritis of Spine—(*Continued*)

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso-Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
9:10 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.5	75	20	
Per cent.	100	17	0	½	70	3	0	0	4	5½						
Number	2,450	417	0	12	1,715	74	0	0	N. 98	134						
9:40 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	1	..	100.2	108	30	Headache
Per cent.	100	50½	0	½	39	2½	2	1	2	2½						
Number	5,350	2,702	0	26	2,087	123	107	25	N. 107	123						
10:10 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.2	108	24	
Per cent.	100	77½	0	0	22½	0	0	0	0	0						
Number	9,150	7,092	0	0	2,058	0	0	0	0	0						
11:10 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.2	93	23	
Per cent.	100	93	0	0	7	0	0	0	0	0						
Number	7,400	6,882	0	0	518	0	0	0	0	0						
12:10 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.6	88	26	
Per cent.	100	87½	0	½	11	0	0	0	½	½						
Number	14,500	12,667	0	73	1,595	0	0	0	B. 72	73						
2:10 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.0	90	26	
Per cent.	100	80	0	0	18½	½	0	0	0	1						
Number	18,300	14,640	0	0	3,385	92	0	0	0	183						
3:10 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	80½	½	0	16	2	1	0	0	0						
Number	16,500	13,282	83	0	2,640	330	165	0	0	0						
4:10 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	Large sausage shap'd	100.0	80	22	
Per cent.	100	77	0	0	14	3	4½	0	0	1½						
Number	9,450	7,276	0	0	1,323	284	425	0	0	142						
5:10 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.0	80	24	Comfortable
Per cent.	100	77½	0	0	15	2	4½	0	½	½						
Number	10,000	7,750	0	0	1,500	200	450	0	50	50						
2/12/18																
2 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.8	78	21	
Per cent.	100	47	1½	½	37½	6½	2½	½	2½	1½						
Number	5,550	2,608	83	28	2,081	361	134	28	N. & B. 134	83						
2/13/18 Third injection Dose 1,000,000,000 T. V.																
8:25 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.4	80	20	Injected at 8:15 a. m.
Per cent.	100	64	½	1	18	10	4	0	0	2½						
Number	7,150	4,576	36	71	1,287	715	286	0	0	179						

8:55 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.4	75	20	8:30, chill lasting 25 minutes
Per cent.	100	56½	0	½	37	½	½	0	1½	3½						
Number	4,250	2,401	0	21	1,573	21	21	0	B. 64	149						
9:25 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.5	91	20	
Per cent.	100	18	0	0	77	3	0	0	1	1						
Number	2,350	423	0	0	1,810	70	0	0	B. 24	23						
9:55 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	1	...	100.6	91	17	Headache
Per cent.	100	67	0	½	25	3	½	½	½	3						
Number	7,250	4,780	0	36	1,813	217	36	36	B. 36	218						
10:25 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.4	120	30	Delirium, severe pain
Per cent.	100	69	0	0	27½	1	½	½	1	½						
Number	3,650	2,520	0	0	1,004	36	18	18	36	18						
11:25 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.8 ax.	124	24	Temp. at knee 101.8
Per cent.	100	85½	0	0	12	0	1½	½	0	½						
Number	5,450	4,660	0	0	654	0	82	27	0	27						
12:25 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.8 ax.	109	26	
Per cent.	100	79	1	0	14	1½	1½	0	½	5						
Number	7,600	6,007	76	0	1,064	115	115	0	B. 38	380						
1:25 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.4	118	34	
Per cent.	100	87	½	½	9	1½	1	0	½	0						
Number	10,150	8,831	51	51	913	152	101	0	E. 51	0						
2:25 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.8	100	32	Rational, more comfortable
Per cent.	100	94	0	0	2	½	½	0	0	3						
Number	15,200	14,288	0	0	304	76	76	0	0	456						
3:25 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.2	100	26	
Per cent.	100	90½	0	0	4½	0	1½	0	½	3						
Number	27,200	24,737	0	0	1,158	0	410	0	B. 136	819						
5:25 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.2	88	22	
Per cent.	100	91½	0	0	6½	½	0	0	0	1½						
Number	11,550	10,569	0	0	750	58	0	0	0	173						
6:25 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.6	84	23	
Per cent.	100	76	½	0	16½	3	1½	0	½	2						
Number	25,250	19,240	126	0	4,216	758	379	0	B. 126	505						
2/14/18																
7:25 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.6	86	18	
Per cent.	100	73½	0	0	16	2	½	0	1½	6½						
Number	9,700	7,130	0	0	1,552	194	48	0	B. 147	630						

TABLE 9.—Case 9. Frances C., Aged 2. Gonorrheal Vulvovaginitis

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso-Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
1/8/18. Control																
4 p. m.																
Number	10,900															
6 p. m.																
Number	12,300															
7 p. m.																
Number	12,800															
8 p. m.											0					
Per cent.	100	49	0	0	48	½	0	0	0	2½						
Number	11,400	5,586	0	0	5,472	57	0	0	0	282						
1/9/18																
First injection																
Dose 1,000,000,000																
T. V.																
6 a. m.											0	...	99.1	104	24	Injected at 8 a. m.
Per cent.	100	63½	0	0	29½	3	0	0	0	4						
Number	11,200	6,112	0	0	3,304	336	0	0	0	448						
8:30 a. m.											0	...	99.8	124	24	
Per cent.	100	61½	½	0	29½	½	5	0	1	2						
Number	7,800	4,797	39	0	2,301	39	390	0	B. 78	156						
9 a. m.											0	..	99.4	84	28	
Per cent.	100	52½	1½	½	40	1½	1	0	½	2½						
Number	6,300	3,308	100	37	2,520	100	63	0	B. 37	164						
9:30 a. m.											0	...	99.8	88	28	
Per cent.	100	57	1	0	34	2	1	0	0	5						
Number	7,100	4,047	71	0	2,414	142	71	0	0	355						
10 a. m.											0	...	100.2	102	26	
Per cent.	100	62½	0	0	34½	½	0	0	½	2						
Number	7,800	4,095	0	0	2,691	39	0	0	B. 39	156						
11 a. m.											0	...	100.2	112	28	
Per cent.	100	64½	½	½	26½	2½	½	0	½	4½						
Number	11,300	7,289	56	56	2,995	283	56	0	B. 56	503						
12 noon											0	...	100.4	98	26	
Per cent.	100	75	0	0	18	2	1½	0	1	2½						
Number	12,000	9,000	0	0	2,160	240	180	0	B. 120	300						
1 p. m.											0	...	100.4	120	28	
Per cent.	100	79	0	0	15½	2½	1	0	0	2						
Number	28,000	22,120	0	0	4,340	700	280	0	0	560						

2 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.7	128	36	
Per cent.	100	78	0	0	16½	1½	½	0	½	3						
Number	18,000	14,040	0	0	2,970	270	90	0	B. 90	540						
3 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.5	124	32	
Per cent.	100	74	0	0	18	0	2	0	0	6						
Number	10,600	7,744	0	0	1,908	0	212	0	0	636						
4 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.5	100	36	
Per cent.	100	87	0	0	10	0	1	0	0	2						
Number	11,000	9,750	0	0	1,100	0	110	0	0	220						
5 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.8	120	36	
Per cent.	100	50½	0	0	44	1	½	0	0	4						
Number	10,900	5,505	0	0	4,796	109	54	0	0	436						
1/10/18																
4:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	64	0	0	27	1	0	0	½	7½						
Number	10,900	6,976	0	0	2,943	109	0	0	B. 55	817						
1/12/18																
Second injection																
Dose 1,000,000,000																
T. V.																
9:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.9	94	24	Injected at 9:30 a. m.
Per cent.	100	57	1	0	34	2	2	0	1	3						
Number	11,300	6,441	113	0	3,842	226	226	0	113	348						
10 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.0	96	24	
Per cent.	100	43	6	0	47	2	1	0	0	2						
Number	7,600	3,268	456	0	3,572	152	76	0	0	152						
10:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	1	...	99.0	96	22	
Per cent.	100	50	2	0	37	4	2	0	2	3						
Number	8,300	4,150	166	0	3,071	332	166	0	E. 166	249						
11 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.2	84	34	
Per cent.	100	61	1	0	30½	5½	1	0	1	0						
Number	8,100	4,941	81	0	2,470	446	81	0	E. 81	0						
11:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	1	...	99.4	84	30	
Per cent.	100	62	0	0	30	2	2	0	0	4						
Number	9,200	5,704	0	0	2,760	184	184	0	0	368						
12 noon	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.4	84	30	
Per cent.	100	60	0	0	40	0	0	0	0	0						
Number	9,200	5,520	0	0	3,680	0	0	0	0	0						
1 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	1	...	99.0	104	32	
Per cent.	100	64	0	0	30	3	3	0	0	1						
Number	13,500	8,640	0	0	4,050	405	405	0	0	135						
2 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.6	108	32	
Per cent.	100	65	1	0	31	2	0	0	0	1						
Number	16,000	10,500	160	0	4,960	320	0	0	0	160						

TABLE 9.—Case 9. Frances C., Aged 2. Gonorrheal Vulvovaginitis—(*Continued*)

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
3 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.0	104	36	
Per cent.	100	65	0	0	25	4	2	0	0	4						
Number	13,400	8,710	0	0	3,350	536	268	0	0	536						
4 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.2	120	30	
Per cent.	100	74	1	0	19	1	1	0	0	4						
Number	13,500	9,990	135	0	2,565	135	135	0	0	540						
5 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.4	112	32	
Per cent.	100	73	0	0	16	6	2	0	1	2						
Number	13,400	9,782	0	0	2,144	804	268	0	B. 134	268						
6 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.4	112	32	
Per cent.	100	74	0	0	22	2	2	0	0	1						
Number	13,500	9,990	0	0	2,970	270	270	0	0	135						
7 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	1	...	99.9	108	32	
Per cent.	100	77	0	0	19	1	1	0	0	2						
Number	11,900	9,163	0	0	2,261	119	119	0	0	238						
1/25/18 Third injection																
10:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	3	...	99.5	92	24	Injected at 10:25 a. m.
Per cent.	100	66	1	0	25	0	0	0	0	8						
Number	12,000	7,920	120	0	3,000	0	0	0	0	960						
12:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.0	132	36	
Per cent.	100	62	0	0	27	2	3	0	1	5						
Number	7,200	4,464	0	0	1,944	144	216	0	B. 72	360						
2:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.2	128	38	
Per cent.	100	77	0	0	10	3	6	0	0	4						
Number	9,400	7,238	0	0	940	282	564	0	0	366						
5:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	2	...	101.0	120	28	
Per cent.	100	78	1	0	4	1	7	0	0	9						
Number	36,900	28,782	369	0	1,476	369	2,723	0	0	3,321						
8:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	3	...	101.0	128	28	
Per cent.	100	75	0	0	10	2	1	0	3	9						
Number	11,300	8,475	0	0	1,130	226	113	0	B. & N. 339	1,017						

1/28/18																
Fourth injection																
11:40 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.1	86	24	Injected 11:40 a. m.
Per cent.	100	69½	1	½	25	1	1	0	½	1½						
Number	11,700	8,132	117	58	2,925	117	117	0	B. 58	176						
1:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.0	136	34	
Per cent.	100	66	2	0	27	2	1	0	1	1						
Number	6,100	4,026	122	0	1,647	122	61	0	B. 61	61						
4 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	2	...	100.6	120	32	
Per cent.	100	74	0	0	10	1	6	0	2	7						
Number	12,800	9,472	0	0	1,280	128	768	0	B. & N. 256	896						
6:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.6	112	28	
Per cent.	100	86	0	0	9	1	1	0	0	3						
Number	15,600	13,416	0	0	1,404	156	156	0	0	468						
8:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.2	104	22	
Per cent.	100	80	0	0	19	1	0	0	0	1						
Number	21,200	16,960	0	0	4,028	212	0	0	0	212						
10:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.6	98	20	
Per cent.	100	83	0	0	16	0	1	0	0	0						
Number	15,300	12,699	0	0	2,448	0	153	0	0	0						
2/1/18																
Fifth injection																
3 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.8	116	30	
Per cent.	100	63	1	0	31	2	3	0	0	0						
Number	7,300	4,597	73	0	2,263	146	219	0	0	0						
5 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.0	106	26	
Per cent.	100	75	0	0	10	2	1	0	1	6						
Number	7,200	5,400	0	0	720	144	72	0	B. 72	432						
7 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	101.0	92	20	
Per cent.	100	75	0	0	22	3	0	0	0	0						
Number	12,400	9,300	0	0	2,728	372	0	0	0	0						
2/17/18																
9:15 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	38	0	0	56	1½	1	0	0	3½						
Number	8,200	3,116	0	0	4,592	99	82	0	0	287						

TABLE 10.—Case 10. Frel., Aged 9. Suppurative Mastoiditis with Chronic Pulmonary Tuberculosis

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
12/21/17 First injection Dose 1,000,000,000 T. V.																
8:45 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	....	...	.....	...	...	Injected at 10 a.m.
Per cent.	100	65	1	0	23	7	2	½	1	½						
Number	19,300	12,545	193	0	4,439	1,351	386	97	B. 193	96						
10:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.4	104	24	
Per cent.	100	74	½	0	14	8	1½	0	1	1						
Number	19,200	14,208	96	0	2,688	1,536	289	0	B. 192	192						
11 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.2	130	28	Chill
Per cent.	100	69	1	0	16	12	0	0	0	2						
Number	17,400	12,006	174	0	2,784	2,088	0	0	0	348						
11:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.4	124	28	
Per cent.	100	61	0	0	35	½	½	0	0	3						
Number	15,300	9,333	0	0	5,355	76	77	0	0	459						
12 noon	.....	.....	....	....	.....	.....	....	...	.....	.....	....	...	103.4	124	28	
Per cent.	100															
Number	16,900															
1 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	105.4	168	34	Emesis
Per cent.	100	97½	0	0	1	½	1	0	0	0						
Number	19,200	18,720	0	0	192	96	192	0	0	0						
2 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	105.0	170	88	Perspiring
Per cent.	100	92	0	0	4½	2	1	0	0	1½						
Number	15,200	13,984	0	0	684	304	152	0	0	228						
3 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	103.0	140	36	
Per cent.	100	88½	0	0	4	3½	1	0	0	3						
Number	22,000	19,740	0	0	880	770	220	0	0	660						
4 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	100.8	132	25	
Per cent.	100	85½	0	½	5	4	0	0	1½	3½						
Number	27,100	23,170	0	136	1,355	1,084	0	0	B. 407	948						
5 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	Large numbers	99.2	122	24	
Per cent.	100	86	0	0	11	½	0	0	0	2½						
Number	29,000	24,940	0	0	3,190	145	0	0	0	725						

6 p. m.	.....	.....	....	....	.....	.....	....	...	.....	... ..	0	...	98.0	130	22	
Per cent.	100	89	0	½	6½	1	1	0	0	2						
Number	30,000	26,700	0	150	1,950	300	300	0	0	600						
7 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	97.6	120	22	
Per cent.	100	88½	0	½	8½	½	½	0	0	1½						
Number	30,100	26,638	0	151	2,558	151	151	0	0	451						
8 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	96.6	115	22	Comfortable
Per cent.	100	80	½	0	11½	4½	1	½	½	1½						
Number	24,800	19,840	124	0	2,852	1,116	248	124	B. 124	124						
9 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	96.3	108	20	
Per cent.	100	71	0	0	21	5	2	0	½	½						
Number	21,000	14,910	0	0	4,410	1,050	420	0	B. 105	105						
10 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	96.3	108	22	
Per cent.	100	80	0	0	14	3	1	0	½	1½						
Number	20,100	16,080	0	0	2,814	603	201	0	B. 100	302						
11 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	96.2	109	22	
Per cent.	100	77	½	½	16½	3	1½	0	½	½						
Number	21,500	16,555	107	108	4,147	645	323	0	B. 107	108						
12 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	96.4	104	22	
Per cent.	100	76½	½	0	19	1	1	½	½	1						
Number	19,300	14,765	96	0	3,667	193	193	96	B. 97	193						
12/22/17																
2 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	96.4	112	24	
Per cent.	100	77½	½	0	16½	2½	1½	0	½	1						
Number	19,800	15,345	99	0	3,267	495	297	0	99	198						
4 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	97.6	120	24	
Per cent.	100	73½	1	0	20½	2½	1	0	½	1						
Number	18,500	13,597	185	0	3,793	462	185	0	93	185						
6 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	97.3	120	24	
Per cent.	100	70	½	0	20½	4	1½	0	1½	2						
Number	20,000	14,000	100	0	4,010	800	300	0	300	400						
8 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	2	...	98.3	124	22	
Per cent.	100	71	1½	½	17½	5½	1½	½	½	½						
Number	18,500	13,135	277	93	3,237	1,018	277	93	93	277						

TABLE 10.—Case 10. Frei., Aged 9. Suppurative Mastoiditis with Chronic Pulmonary Tuberculosis—(*Continued*)

Date and Hour	Total Leukocytes	Polys.	Eosin. Polys.	Baso. Polys.	Small Lymph.	Large Lymph.	Transitionals	Mast Cells	Myelocytes	Atypicals	Nucleated Reds	Platelets	Temperature	Pulse	Respiration	Clinical
12/31/17																
Control counts																
9 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	69	0	½	23½	3	2	0	0	2						
Number	17,200	11,868	0	86	4,042	516	344	0	0	344						
10 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	72	½	½	15	4½	3	0	1½	2						
Number	17,300	12,456	87	86	2,595	779	519	0	B. 259	519						
11 a. m.	.....	.....	....	....	.. .	.....	....	...	.....	.....	0					
Per cent.	100	74	½	0	11	10	4½	0	0	0						
Number	17,700	13,098	89	0	1,957	1,770	796	0	0	0						
12 noon	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	70	1	0	22	5	2	0	0	0						
Number	20,700	14,490	207	0	4,554	1,035	414	0	0	0						
1 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	64½	0	0	26½	5	1	0	0	0						
Number	22,000	14,577	0	0	5,989	1,130	226	0	0	0						
2 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	80	0	0	18½	½	½	0	C	½						
Number	17,900	14,320	0	0	3,311	90	89	0	0	90						
3 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	73	0	½	22	2	1	0	0	1½						
Number	20,600	15,038	0	103	4,532	412	206	0	0	309						
6 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	60	½	0	36	2	1½	0	0	0						
Number	23,100	13,860	115	0	8,316	462	347	0	0	0						
1/1/18																
Second injection																
Dose 1,000,000,000 T. V.																
7:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.0	132	20	Injected at 7:30 a. m.
Per cent.	100	70	0	½	25	3½	1	0	0	½						
Number	21,000	14,700	0	105	5,250	735	210	0	0	105						
8 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.0	132	24	
Per cent.	100	68	0	½	25	3½	½	0	½	2						
Number	13,300	9,044	0	66	3,215	466	66	0	B. 67	266						

8:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.2	122	24	
Per cent.	100	53	0	½	42	2	1	½	0	1						
Number	4,100	2,173	0	20	881	82	41	21	0	41						
9 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	99.6	132	32	
Per cent.	100	60	0	0	38	½	½	0	0	1						
Number	6,100	3,660	0	0	2,318	30	31	0	0	61						
9:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	102.0	164	32	Chill for 15 min.
Per cent.	100	62	0	0	36	0	½	0	½	1						
Number	15,900	9,858	0	0	5,724	0	80	0	B. 79	159						
10 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0					
Per cent.	100	93	0	0	5½	½	½	0	0	½						
Number	39,300	36,549	0	0	2,161	197	197	0	0	196						
10:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	..	102.2	160	32	
Per cent.	100	89	0	0	9	0	0	0	0	2						
Number	31,600	28,124	0	0	2,844	0	0	0	0	632						
11:30 a. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	..	99.2	132	28	
Per cent.	100	93	0	0	2	1	1	0	0	3						
Number	29,600	27,528	0	0	592	296	296	0	0	888						
12:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	1	...	98.4	132	24	
Per cent.	100	91	0	½	6	½	½	0	½	1						
Number	36,100	32,851	0	180	2,166	181	180	0	B. 181	361						
1:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.4	132	24	
Per cent.	100	80	0	0	14	½	1½	0	1	3						
Number	34,800	27,840	0	0	4,872	174	522	0	348	1,044						
2:30 p. m.	.....	.....	....	....	.....	.....	...	...	.....	.....	0	...	98.7	130	24	
Per cent.	100	86	½	0	10½	½	½	0	½	1½						
Number	33,100	28,466	165	0	3,476	165	166	...	B. 165	497						
3:30 p. m.	.....	.....	....	....	.....	.....	...	...	.....	.....	0	...	98.5	124	26	
Per cent.	100	84	0	0	13	1	½	0	0	1½						
Number	26,800	22,512	0	0	3,484	268	134	0	0	402						
4:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	1	...	98.2	124	24	
Per cent.	100	80	0	0	15	1½	½	0	½	2½						
Number	24,000	19,200	0	0	3,600	360	120	0	B. 120	600						
5:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.4	120	24	
Per cent.	100	76½	½	0	18	2	1	½	½	1						
Number	22,500	17,213	112	0	4,050	450	225	113	B. 112	225						
6:30 p. m.	.....	.....	....	....	.....	.....	....	...	.....	.....	0	...	98.8	128	24	
Per cent.	100	82	½	0	11½	2½	1	½	½	1½						
Number	22,000	18,040	110	0	2,530	550	220	110	B. 110	330						